Supporting Information

A Facile Synthesis of 5-Amino-[1,2,3]triazolo[5,1-*a*]isoquinoline Derivatives through Copper-Catalyzed Cascade Reactions

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I. General Methods and materials:

All of the reactions dealing with air and/or moisture-sensitive reactions were carried out under an atmosphere of argon using pear-shaped Schlenk flask and standard syringe/septa techniques. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 600 MHz and 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (TMS) (0.00 ppm) or $CDCl_3$ (7.26 ppm) for ^{1}H, $CDCl_3$ (77.0 ppm) for ^{13}C and d^6-DMSO (2.5 ppm) for ^{1}H, (39.5 ppm) for ^{13}C. Flash column chromatography was performed on 200-300 mesh silica gel. Analytical thin layer chromatography was performed with precoated glass baked plates (250μ) and visualized by fluorescence. MS were measured on a Finnigan Trace MS spectrometer; HRMS were recorded on LTQ-FTUHRA and Bruker Apex IV FTMS spectrometer. Melting points were measured on a melting point tester RY-1G apparatus and uncorrected.

II. Experimental

The nitrostyrenes were synthesized according to the literatures as below:

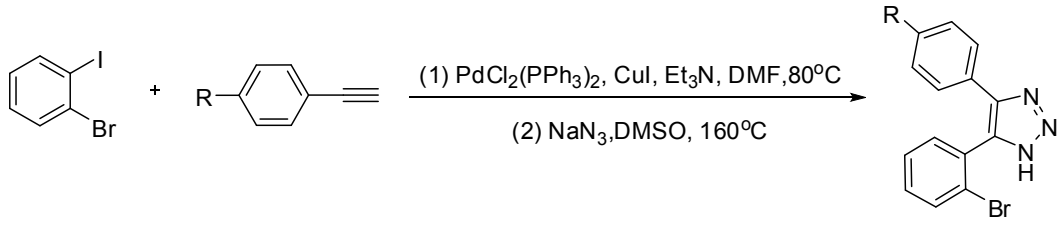
1. Ming-Yu Wu; Ming-Qi Wang; Kun Li; Xing-Wen Feng; Ting He; Na Wang; Xiao-Qi Yu. *Tetrahedron Lett*. **2011**, *52*, 679-683.

2. Béatrice Quiclet-Sire; Samir Z. Zard. *Synthesis*. **2005**, *19*, 3319-3326.

Typical experimental procedure for synthesis of **1a**, **1b**, **1c**, **1f**, **1g** and **1h**.

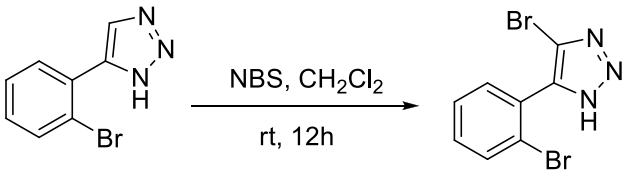
A solution of nitrostyrene in DMSO was added dropwise over 12 h to a hot (80-90 °C) solution of NaN_3 in DMSO (0.1M). The mixture was cooled and poured into water, then extract with EtOAc, and the combined organic layer further washed with brine and dried with Na_2SO_4. Concentration under reduced pressure and purification of the residue by flash chromatography on silica gel or purified by simple recrystallization.

Representative experimental procedure for synthesis of **1d** and **1e**.



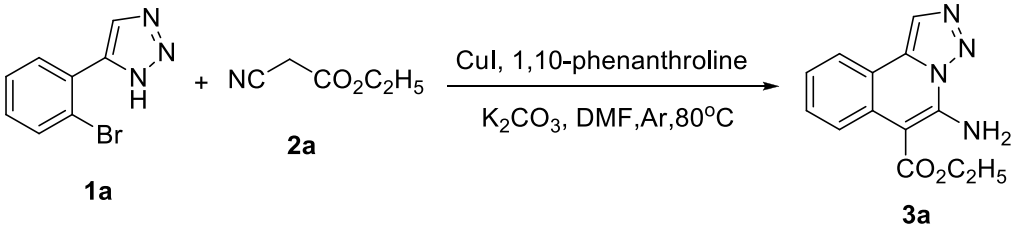
1-Bromo-2-iodobenzene, $PdCl_2(PPh_3)_2$, CuI were added to a pear-shaped Schlenk tube charged with a magnetic stirrer. The tube was evacuated and backfilled with argon and then degassed Et_3N and DMF was introduced, then the terminal alkyne was introduced, the mixtures were heating at 80 °C for 4-5 hours. Then poured into water and extracted with EtOAc, the organic layer further washed with brine and dried with anhydrous Na_2SO_4. After filtration, the organic layer was concentrated under reduced pressure and the residue was purified by short flash column chromatography (silica gel) to give oil. The oil and NaN_3 were dissolved in DMSO, the solution was heating at 160°C. The reaction was monitored by TLC, after the completion of the reaction, the mixture poured into water and extracted with EtOAc. The organic layer was washed with brine and dried with anhydrous Na_2SO_4. Concentration under reduced pressure and purification of the residue by flash chromatography on silica gel gives the target product.

Experimental procedure for synthesis of **1i**.



To a solution of (1.00 g, 4.46 mmol) in dichloromethane (20 mL, 0.2 M), was added N-Bromo-succinimide (1.19 g, 6.69 mmol). The reaction mixture was stirred at room temperature, and monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/ petroleum ether, V/V, 1:7) to give (yield: 1.25 g, 92.6%) as colorless crystals.

Representative experimental procedure for synthesis of **3a**.

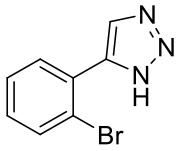


1a **2a** **3a**

Substituted 5-(2-bromophenyl)-*1H*-1,2,3-triazole (112 mg, 0.5 mmol) and CuI (10 mg, 0.05 mmol), K_2CO_3 (104 mg, 0.75 mmol), 1,10-phenanthroline (18 mg, 0.1 mmol) were added to a pear-shaped Schlenk tube charged with a magnetic stirrer. The tube was evacuated and backfilled with argon and then DMSO (2.0 mL) and ethyl 2-cyanoacetate (85 mg, 0.75 mmol) were added to the tube under a stream of argon. The tube was sealed and the mixture was stirred at 80 °C under an argon atmosphere. The reaction was monitored by TLC (about 4h), after completion of the reaction, the mixture was diluted with EtOAc, then washed with water and extracted with EtOAc .The combined organic layer was washed with brine then dried with anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give a residue, the residue was purified by column chromatography on silica gel to provide the **3a** as white solid (118 mg, yield: 92%).

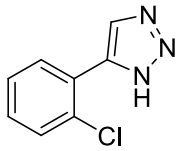
III. Compounds Characterization

5-(2-bromophenyl)-1H-1,2,3-triazole (**1a**)



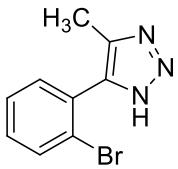
White solid, mp: 83-85℃,^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.68 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.6, 133.5, 130.8, 129.9, 129.7, 127.7, 127.6, 121.8; ESI-MS(m/z): 222.9$[M]^+$, 224.9 $[M+2]^+$(1:1). HRMS (ESI) calcd. For $C_8H_6BrN_3$+H^+ 223.9818. found 223.9817.

5-(2-chlorophenyl)-1H-1,2,3-triazole (**1b**)



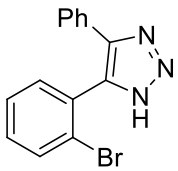
White solid, mp: 92-96□, ^{1}H NMR (400 MHz, d^6-DMSO) δ 8.35 (s, 1H), 7.92 (s, 1H), 7.54 (d, *J* = 10.4 Hz, 1H), 7.43-7.35 (m, 2H); ^{13}C NMR (100 MHz, d^6-DMSO) δ 131.0, 130.3, 129.7, 129.3, 127.5; ESI-MS(m/z):179.2$[M]^+$, 178.2$[M-1]^+$ (3:1); HRMS (ESI) calcd. For $C_8H_6ClN_3$+H^+ 180.0323. found 180.0322.

5-(2-bromophenyl)-4-methyl-1H-1,2,3-triazole (**1c**)



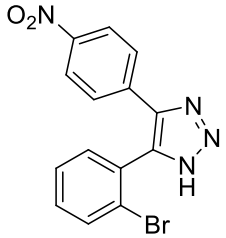
White solid, mp: 136-138□, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 4.8 Hz, 1H), 7.31-7.25 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 132.0, 131.5, 130.3, 127.3, 123.7, 10.3; ESI-MS(m/z):237.1$[M]^+$, 239.1$[M+2]^+$(1:1); HRMS (ESI) calcd. For $C_9H_8BrN_3$+H^+ 237.99744. found 237.99741.

5-(2-bromophenyl)-4-phenyl-1H-1,2,3-triazole (**1d**)



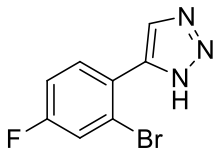
Yellow oil.^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.35 (s, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.20-7.11 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.1, 133.1, 132.2, 132.0, 130.6, 130.4, 128.7, 128.5, 128.2, 127.6, 127.4, 126.9, 126.8, 124.0; ESI-MS(m/z): 299.0[M]+, 301.0[M+2]+(1:1). ESI-MS(m/z): 299.0$[M]^+$, 301.0$[M+2]^+$(1:1). HRMS (ESI) calcd. For $C_{14}H_{10}BrN_3$+H^+ 300.0131. found 300.0128.

5-(2-bromophenyl)-4-(4-nitrophenyl)-1H-1,2,3-triazole (**1e**)



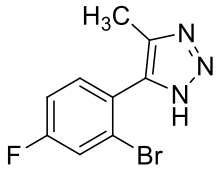
Yellow solid, mp: 165-169□, ^{1}H NMR (600 MHz, d^{6}-DMSO) δ 8.20 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.55-7.47 (m, 3H); ^{13}C NMR (150 MHz, d^{6}-DMSO) δ 146.8, 133.2, 133.1, 132.4, 132.3, 131.6, 128.43, 128.37, 126.9, 125.2, 124.3, 124.1, 123.4, 123.2; ESI-MS(m/z): 344.0[M]$^{+}$, 346.0 [M+2]$^{+}$(1:1); HRMS (ESI) calcd. For $C_{14}H_9BrN_4O_2$+H^{+} 344.9982. found 344.9981.

5-(2-bromo-4-fluorophenyl)-1H-1,2,3-triazole (**1f**)



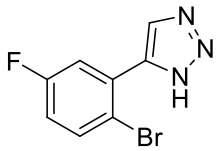
White solid, mp: 128-130□, ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.80 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, d^{6}-DMSO) δ 161.5(d, *J* = 248 Hz, 1C) 132.3, 128.2, 121.9, 120.5(d, *J* = 25 Hz, 1C), 115.3(d, *J* = 21 Hz, 1C), 109.7; ESI-MS(m/z): 241.0[M]$^{+}$, 243.0[M+2]$^{+}$(1:1); HRMS (ESI) calcd. For $C_8H_5BrFN_3$+H^{+} 241.9724. found 241.9723.

5-(2-bromo-4-fluorophenyl)-4-methyl-1H-1,2,3-triazole (**1g**)



White solid, mp: 127-129□, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.37 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.14-7.08 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5(d, *J* = 252 Hz, 1C), 133.1, 133.0, 127.8, 124.2, 124.1, 120.4(d, *J* = 25 Hz, 1C), 114.8(d, *J* = 21 Hz, 1C), 10.1; ESI-MS(m/z):255.1[M]$^{+}$, 257.1[M+2]$^{+}$(1:1); HRMS (ESI) calcd. For $C_9H_7BrFN_3$+H^{+} 255.98801. found 255.98796.

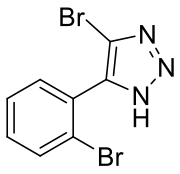
5-(2-bromo-5-fluorophenyl)-1H-1,2,3-triazole (**1h**)



White solid, mp: 155-156□, ^{1}H NMR (400 MHz, d^{6}-DMSO) δ 8.41 (s, 1H), 7.79-7.50 (m, 2H), 7.16 (s, 1H); ^{13}C NMR (100 MHz, d^{6}-DMSO) δ 161.3(d, *J* = 243 Hz, 1C), 135.4, 135.3, 133.4, 117.1(t, *J* = 21 Hz, 1C), 115.6; ESI-MS(m/z): 241.1[M]$^{+}$, 243.1[M+2]$^{+}$ (1:1); HRMS (ESI) calcd.

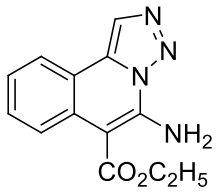
For $C_8H_5BrFN_3$+H^+ 241.9724. found 241.9725.

4-bromo-5-(2-bromophenyl)-1H-1,2,3-triazole (**1i**)



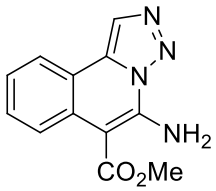
White solid, mp: 152-155□, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.45-7.39 (m, 2H), 7.36-7.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 132.0, 131.1, 127.4, 123.6; ESI-MS(m/z): 300.8$[M]^+$, 302.9$[M+2]^+$, 304.9$[M+4]^+$(1:2:1); HRMS (ESI) calcd. For $C_8H_5Br_2N_3$+H^+ 301.8923. found 301.8924.

ethyl 5-amino-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3a**)



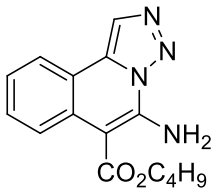
White solid, mp: 161-162℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.4 Hz, 1H), 8.37 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.77 (s, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 4.53 (q, *J* = 7.8 Hz, 2H), 1.52 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 144.1, 133.2, 129.7, 129.5, 129.4, 125.5, 125.3, 124.2, 124.1, 116.3, 61.2, 14.9; ESI-MS(m/z): 257.1$[M]^+$; HRMS (ESI) calcd. For $C_{13}H_{12}N_4O_2$+H^+ 257.10330. found 257.10330.

methyl 5-amino-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3b**)



White solid, mp: 180-182℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.4 Hz, 1H), 8.40 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.79 (s, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 144.3, 133.3, 129.8, 129.4, 126.2, 125.5, 124.4, 124.1, 116.4, 52.0; ESI-MS(m/z): 242.0$[M]^+$; HRMS (ESI) calcd. For $C_{12}H_{10}N_4O_2$+H^+ 243.0877. found 243.0876.

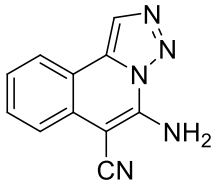
tert-butyl 5-amino-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3c**)



White solid, mp: 129-131℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.39 (s, 1H),

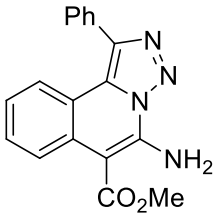
8.04 (d, *J* = 7.8 Hz, 1H), 7.68 (s, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 8.4 Hz, 1H), 1.72 (s, 9H). 13C NMR (75 MHz, $CDCl_3$) δ 167.6, 143.7, 133.1, 129.8, 126.6, 125.5, 124.2, 124.0, 116.4, 82.8, 28.6; ESI-MS(m/z): 284.1$[M]^+$; HRMS (ESI) calcd. For $C_{15}H_{16}N_4O_2$+H^+ 285.13460. found 285.13463.

methyl 5-amino-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3d**)



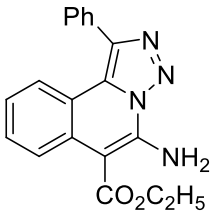
White solid, mp: 232-234℃, ^{1}H NMR (600 MHz, d^6-DMSO) δ 8.83 (s, 1H), 8.52 (s, 2H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 2H), 7.45 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, d^6-DMSO) δ 145.3, 133.2, 130.4, 129.3, 127.8, 127.7, 124.7, 121.7, 116.1, 115.3; ESI-MS(m/z): 209.1$[M]^+$; HRMS (ESI) calcd. For $C_{11}H_7N_5$+H^+ 210.07742. found 210.07735.

methyl 5-amino-1-phenyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3e**)



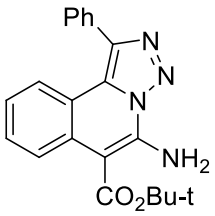
White solid, mp: 198-200□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.79-7.73 (m, 4H), 7.59-7.49 (m, 4H), 7.21-7.16 (m, 1H), 3.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 144.1, 141.9, 131.7, 129.7, 129.54, 129.49, 129.4, 128.9, 128.8, 128.7, 125.4, 123.9, 117.2, 52.1; ESI-MS(m/z): 319.0$[M]^+$; HRMS (ESI) calcd. For $C_{18}H_{14}N_4O_2$+H^+ 319.11895. found 319.11897.

ethyl 5-amino-1-phenyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3f**)



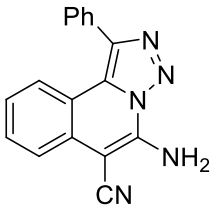
White solid, mp: 163-166□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.77-7.50 (m, 4H), 7.58-7.52 (m, 4H), 7.20 (t, *J* = 7.6 Hz, 1H), 4.55 (q, *J* = 7.8 Hz, 2H), 1.52 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 144.0, 141.9, 131.7, 129.7, 129.4, 128.9, 128.8, 128.7, 125.4, 123.9, 123.3, 117.3, 61.3, 14.4; ESI-MS(m/z): 332.4$[M]^+$; HRMS (ESI) calcd. For $C_{19}H_{16}N_4O_2$+H^+ 333.1346. found 333.1347.

tert-butyl 5-amino-1-phenyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3g**)



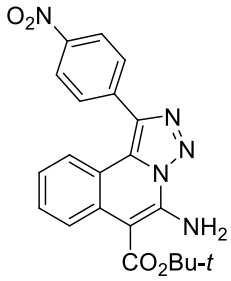
White solid, mp: 177-179□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.76-7.73 (m, 2H), 7.67(s, 2H), 7.58-7.48 (m, 4H), 7.20-7.15(m, 1H), 1.72 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 143.5, 141.8, 131.8, 129.9, 129.7, 129.1, 128.8, 128.6, 125.4, 123.8, 123.7, 117.3, 82.9, 28.6; ESI-MS(m/z): 360.95$[M]^+$; HRMS (ESI) calcd. For $C_{21}H_{20}N_4O_2+H^+$ 361.1659. found 361.1660.

5-amino-1-phenyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carbonitrile (**3h**)



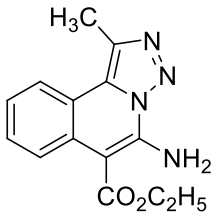
White solid, mp: 233-234□. ^{1}H NMR (600 MHz, d^6-DMSO) δ 8.58 (s, 2H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.72-7.70 (m, 3H), 7.64-7.57 (m, 4H), 7.27 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, d^6-DMSO) δ 145.2, 141.4, 131.2, 129.7, 129.6, 129.2, 129.0, 128.5, 122.9, 116.1, 115.8; ESI-MS(m/z): 285.2 $[M]^+$; HRMS (ESI) calcd. For $C_{17}H_{11}N_5+H^+$ 286.10872. found 286.10871.

tert-butyl 5-amino-1-(4-nitrophenyl)-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3i**)



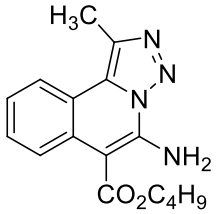
Yellow solid, mp: 187-189□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 2H), 7.58-7.55 (m, 1H), 7.27-7.22 (m, 1H), 1.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 147.9, 143.3, 139.5, 138.6, 130.5, 130.4, 129.9, 129.3, 125.8, 124.1, 124.1, 123.1, 116.6, 83.2, 28.6; ESI-MS (m/z): 405.10$[M]^+$; HRMS (ESI) calcd. For $C_{21}H_{19}N_5O_4+H^+$ 406.1510. found 406.1511.

ethyl 5-amino-1-methyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3j**)



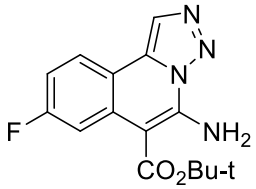
White solid, mp: 195-196□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.72 (s, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 4.54 (d, *J* = 7.8 Hz, 2H), 2.90 (s, 3H), 1.52 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 144.1, 137.3, 129.3, 128.9, 128.7, 125.3, 124.2, 123.5, 123.3, 117.9, 61.2, 29.7, 14.0; ESI-MS(m/z): 284.1$[M]^+$; HRMS (ESI) calcd. For $C_{14}H_{14}N_4O_2$+H^+ 271.1190. found 270.1186.

tert-butyl 5-amino-1-methyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3k**)



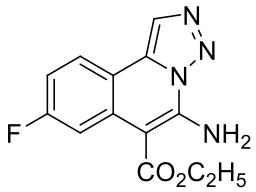
White solid, mp: 130-135□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 13.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 2H), 7.14 (t, *J* = 8.4 Hz, 1H), 2.87 (s, 3H), 1.73 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) 167.5, 143.5, 137.1, 129.4, 128.6, 128.4, 128.2, 125.2, 123.8, 123.2, 117.8, 82.6, 28.6, 13.4; ESI-MS(m/z): 298.2$[M]^+$; HRMS (ESI) calcd. For $C_{16}H_{18}N_4O_2$+H^+ 299.1503. found 299.1506.

tert-butyl 5-amino-8-fluoro-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3l**)



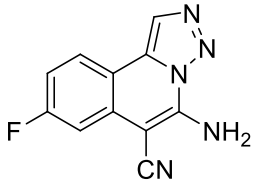
White solid, mp: 172-174℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 13.2, 2.4 Hz, 1H), 8.33 (s, 1H), 8.00 (dd, *J* =13.2, 2.4 Hz, 1H), 7.85 (s, 2H), 7.16-7.10 (m, 1H), 1.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 163.2(d, *J* = 245 Hz, 1C), 144.6, 132.7, 132.0, 131.8, 126.2, 126.0(d, *J* = 9Hz, 1C), 112.9, 112.7(d, *J* = 24 Hz, 1C), 111.5(d, *J* = 27 Hz, 1C), 83.3, 28.5; ESI-MS(m/z): 302.2$[M]^+$; HRMS (ESI) calcd. For $C_{15}H_{15}FN_4O_2$+H^+ 303.1252. found 303.1253.

ethyl 5-amino-8-fluoro-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3m**)



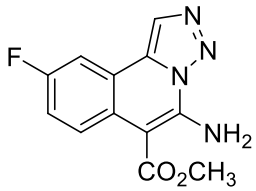
White solid, Mp: 189-190□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 10.8, 3.0 Hz, 1H), 8.35 (s, 1H), 8.02 (dd, *J* = 8.6, 6.1 Hz, 1H), 7.93 (s, 2H), 7.16 (dd, *J* = 10.8, 3.0 Hz, 1H), 4.55 (q, *J* = 7.8 Hz, 2H), 1.54 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 163.4(d, *J* = 248 Hz, 1C), 145.0, 132.9, 126.4, 126.2(d, *J* = 9 Hz, 1C), 112.97, 112.96(d, *J* = 24 Hz, 1C), 112.8, 111.7(d, *J* = 26 Hz, 1C), 61.5, 14.4; ESI-MS(m/z):274.3$[M]^+$; HRMS (ESI) calcd. For $C_{13}H_{11}FN_4O_2$ +H^+ 275.09388. found 275.09387.

5-amino-8-fluoro-[1,2,3]triazolo[5,1-a]isoquinoline-6-carbonitrile (**3n**)



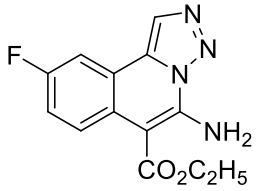
White solid, mp: 265-268□. ^{1}H NMR (600 MHz, d^6-DMSO) δ 8.74 (s, 1H), 8.62 (s, 2H), 8.30 (s, 1H), 7.28 (s, 2H); ^{13}C NMR (100 MHz, d^6-DMSO) δ 163.0(d, *J* = 246 Hz, 1C), 145.7, 132.8, 131.8(d, *J* = 10 Hz, 1C), 127.7, 127.6, 127.4, 115.7, 113.0(d, *J* = 24 Hz, 1C), 112.1, 106.9(d, *J* = 25 Hz, 1C); ESI-MS(m/z): 227.2$[M]^+$; HRMS (ESI) calcd. For $C_{11}H_6FN_5$+H^+ 228.0680. found 228.0679.

methyl 5-amino-9-fluoro-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3o**)



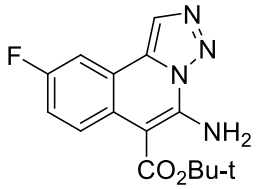
White solid, mp: 195-198□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 9.6, 5.4 Hz, 1H), 8.37 (s, 1H), 7.75 (s, 2H), 7.67 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.35-7.28 (m, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 159.2(d, *J* = 245 Hz, 1C), 143.9, 132.6, 128.1(d, *J* = 7 Hz, 1C), 127.2, 125.9, 118.2(d, *J* = 22 Hz, 1C), 117.2, 117.4, 109.3(d, *J* = 23 Hz, 1C), 52.1; ESI-MS(m/z): 260.2$[M]^+$; HRMS (ESI) calcd. For $C_{12}H_9FN_4O_2$+H^+ 261.07823. found 261.07824.

ethyl 5-amino-9-fluoro-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3p**)



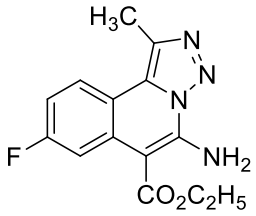
White solid, mp: 167-169□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.36 (s, 1H), 7.73 (s, 2H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.30 (s, 1H), 4.54 (q, *J* = 7.8 Hz, 2H), 1.52 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 159.2(d, *J* = 245 Hz, 1C), 143.8, 132.6, 128.1(d, *J* = 8 Hz, 1C), 127.2, 126.0, 118.1(d, *J* = 22 Hz, 1C), 117.5(d, *J* = 9 Hz, 1C), 110.0, 109.3(d, *J* = 22 Hz, 1C), 61.5, 14.4; ESI-MS(m/z): 274.2$[M]^+$; HRMS (ESI) calcd. For $C_{13}H_{11}FN_4O_2$+H^+ 275.0939. found 275.0940.

tert-butyl 5-amino-9-fluoro-1-methyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3q**)



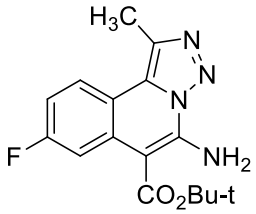
White solid, mp: 155-157□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 9.6, 5.4 Hz, 1H), 8.36 (s, 1H), 7.68-7.63(m, 3H), , 7.33-7.25 (m, 1H), 1.72 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 167.3, 159.2(d, *J* = 245 Hz, 1C), 143.4, 132.4, 128.1 (d, *J* = 10 Hz, 1C), 127.1, 126.3, 126.2, 117.9(d, *J* = 22 Hz, 1C), 117.5(d, *J* = 23 Hz, 1C), 109.2(d, *J* = 23 Hz, 1C), 83.3, 28.5; ESI-MS(m/z): 302.3$[M]^+$; HRMS (ESI) calcd. For $C_{15}H_{15}FN_4O_2$+H^+ 303.12518. found 303.12532.

ethyl 5-amino-8-fluoro-1-methyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3r**)



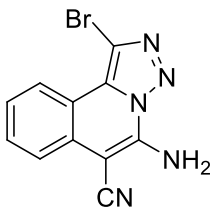
White solid, mp: 192-193□. ^{1}H NMR (600 MHz, d^6-DMSO) δ 8.34 (s, 3H), 8.05 (s, 1H), 7.13 (s, 1H), 4.50 (q, *J* = 7.8 Hz, 2H), 2.82 (s, 3H), 1.50 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, d^6-DMSO) δ 167.2, 160.0(d, *J* = 241 Hz, 1C), 144.6, 136.4, 131.6, 128.0, 126.1, 113.8, 112.0(d, *J* = 25 Hz, 1C), 110.0(d, *J* = 27 Hz, 1C), 61.1. 14.2, 12.9; ESI-MS(m/z): 288.3$[M]^+$; HRMS (ESI) calcd. For $C_{14}H_{13}FN_4O_2$+H^+ 289.1095. found 289.1094.

tert-butyl 5-amino-8-fluoro-1-methyl-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3s**)



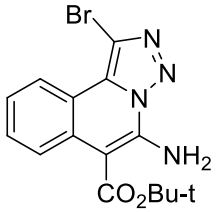
White solid, mp: 167-170□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 13.2 Hz, 1H), 8.09 – 8.03 (m, 1H), 7.81 (s, 2H), 7.15 (t, *J* = 8.4 Hz, 1H), 2.87 (s, 3H), 1.73 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ167.3, 162.6(d, *J* = 244 Hz, 1C), 144.5, 131.8, 131.7, 125.3, 125.2, 114.5, 114.4, 112.3(d, *J* = 24 Hz, 1C), 111.5(d, *J* = 27 Hz, 1C), 83.2, 28.6, 13.4; ESI-MS(m/z): 316.3$[M]^+$; HRMS (ESI) calcd. For $C_{16}H_{17}FN_4O_2$+H^+ 317.1408. found 317.1409.

5-amino-1-bromo-[1,2,3]triazolo[5,1-a]isoquinoline-6-carbonitrile (**3t**)



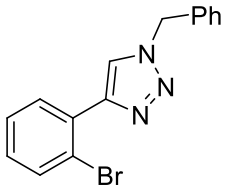
White solid, mp > 240□ (decomp). ^{1}H NMR (600 MHz, d^6-DMSO) δ 8.59 (s, 2H), 8.57 (s, 1H), 7.72-7.65 (m, 2H), 7.49-7.45 (m, 1H); ^{13}C NMR (100 MHz, d^6-DMSO) δ 144.8, 130.8, 129.8, 128.9, 124.6, 122.7, 121.9, 115.8, 114.7, 113.8, 71.6; ESI-MS(m/z): 287.2[M]$^+$, 289.3[M+2]$^+$ (1:1) ; HRMS (ESI) calcd. For $C_{11}H_6BrN_5$+H$^+$ 287.98793. found 287.98787.

tert-butyl 5-amino-1-bromo-[1,2,3]triazolo[5,1-a]isoquinoline-6-carboxylate (**3u**)



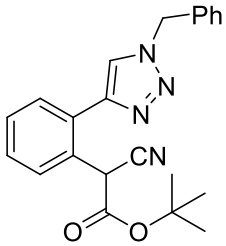
White solid, mp: 152-155□. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (d, *J* = 8.4 Hz, 1H), 8.68 (d, *J* = 9.0 Hz, 1H), 7.64-7.59 (m, 1H), 7.57 (s, 2H), 7.48-7.44 (m, 1H), 1.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 142.8, 129.7, 129.6, 128.6, 125.1, 124.0, 122.8, 116.0, 113.5, 83.1, 28.6; ESI-MS(m/z): 362.1[M]$^+$, 364.1[M+2]$^+$ (1:1); HRMS (ESI) calcd. For $C_{15}H_{15}BrN_4O_2$+H$^+$ 363.0451. found 363.0453.

1-benzyl-4-(2-bromophenyl)-1H-1,2,3-triazole (**4**)



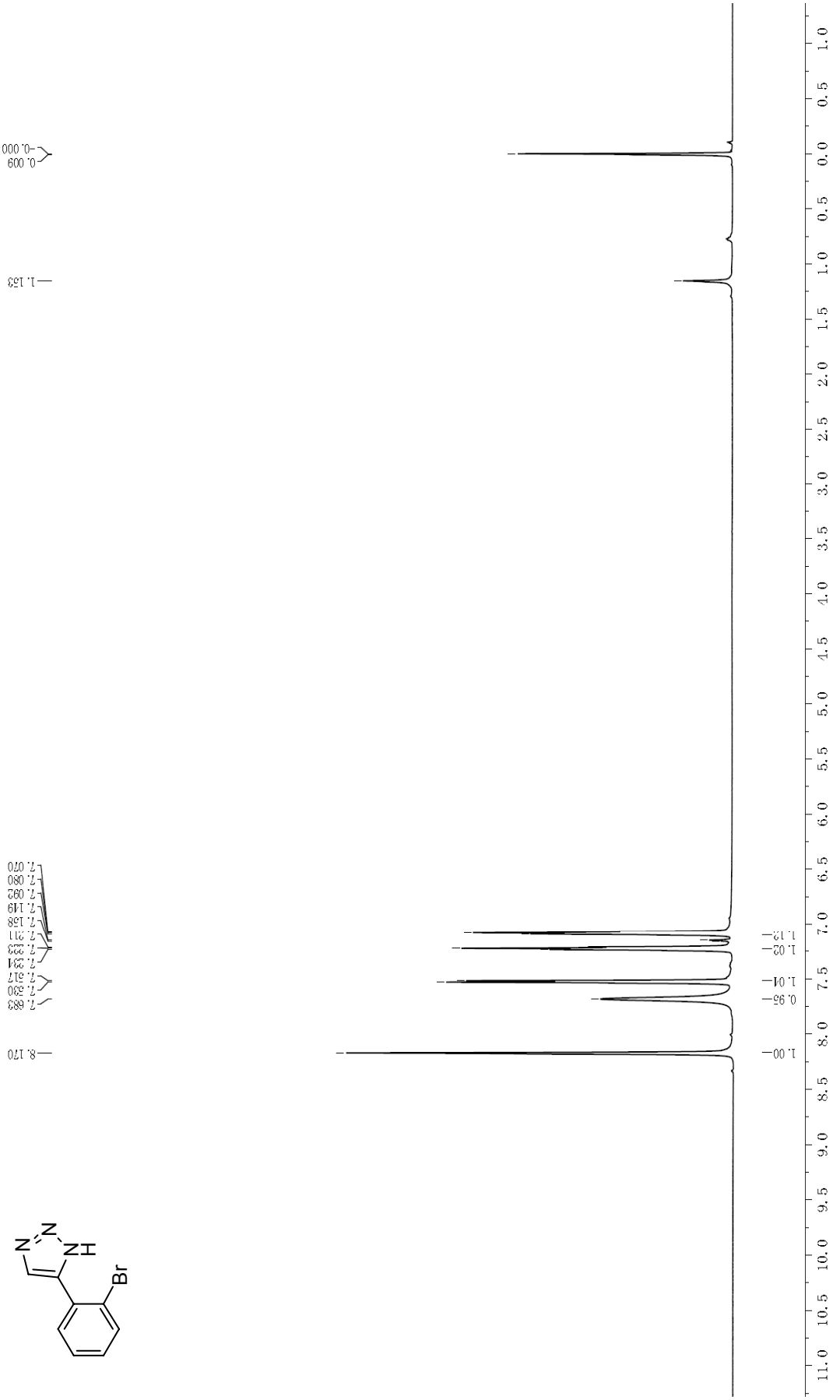
White solid, mp: 78-79□, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.07 (m, 2H), 7.61 (d, *J* = 3.6 Hz, 1H), 7.39-7.29 (m, 5H), 7.19-7.13 (m, 1H), 5.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 134.6, 133.4, 131.2, 130.5, 129.2, 129.0, 128.6, 127.8, 127.6, 123.0, 121.1, 54.1; ESI-MS(m/z): 312.9 [M]$^+$, 314.9[M+2]$^+$ (1:1); HRMS (ESI) calcd. For $C_{15}H_{12}BrN_3$+H$^+$ 314.0287. found 314.0289.

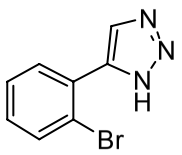
tert-butyl 2-(2-(1-benzyl-1H-1,2,3-triazol-4-yl)phenyl)-2-cyanoacetate (**5**)



Yellow oil，^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.50-7.29 (m, 8H), 6.07 (s, 1H), 5.57 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 147.0, 134.3, 129.3, 129.2, 129.0, 128.1, 121.9, 116.8, 84.1, 54.3, 41.8, 27.6; ESI-MS(m/z): 374.4[M]$^+$; HRMS (ESI) calcd. For $C_{22}H_{22}N_4O_2$+H$^+$ 375.18155. found 375.18163.

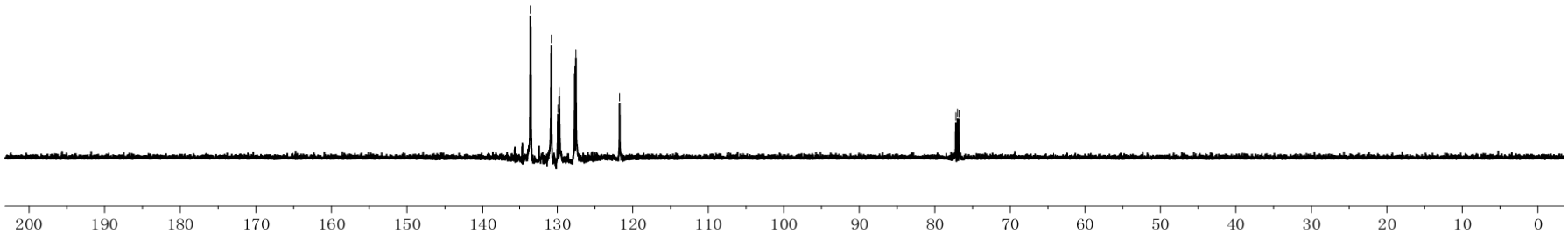
IV. NMR spectra data

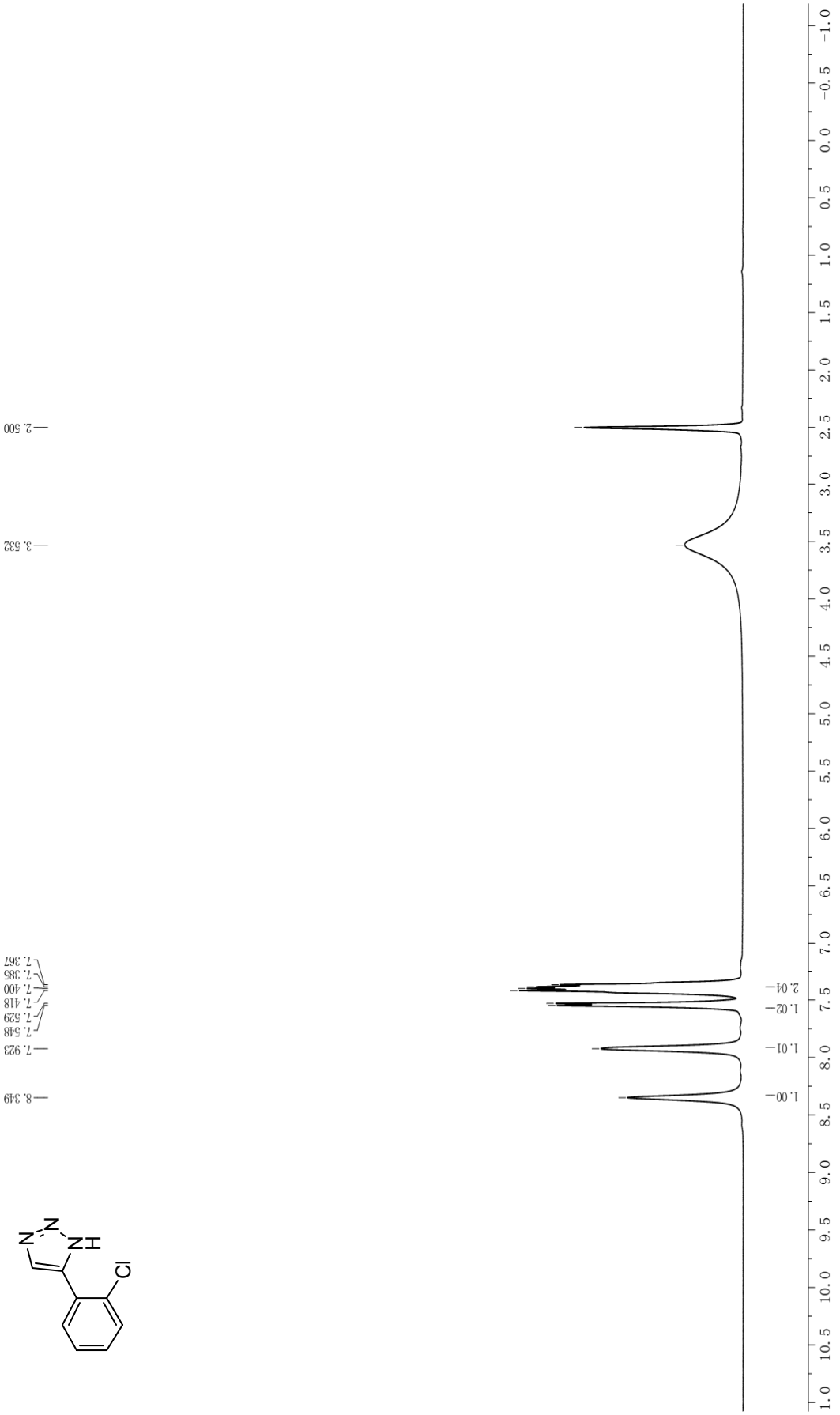


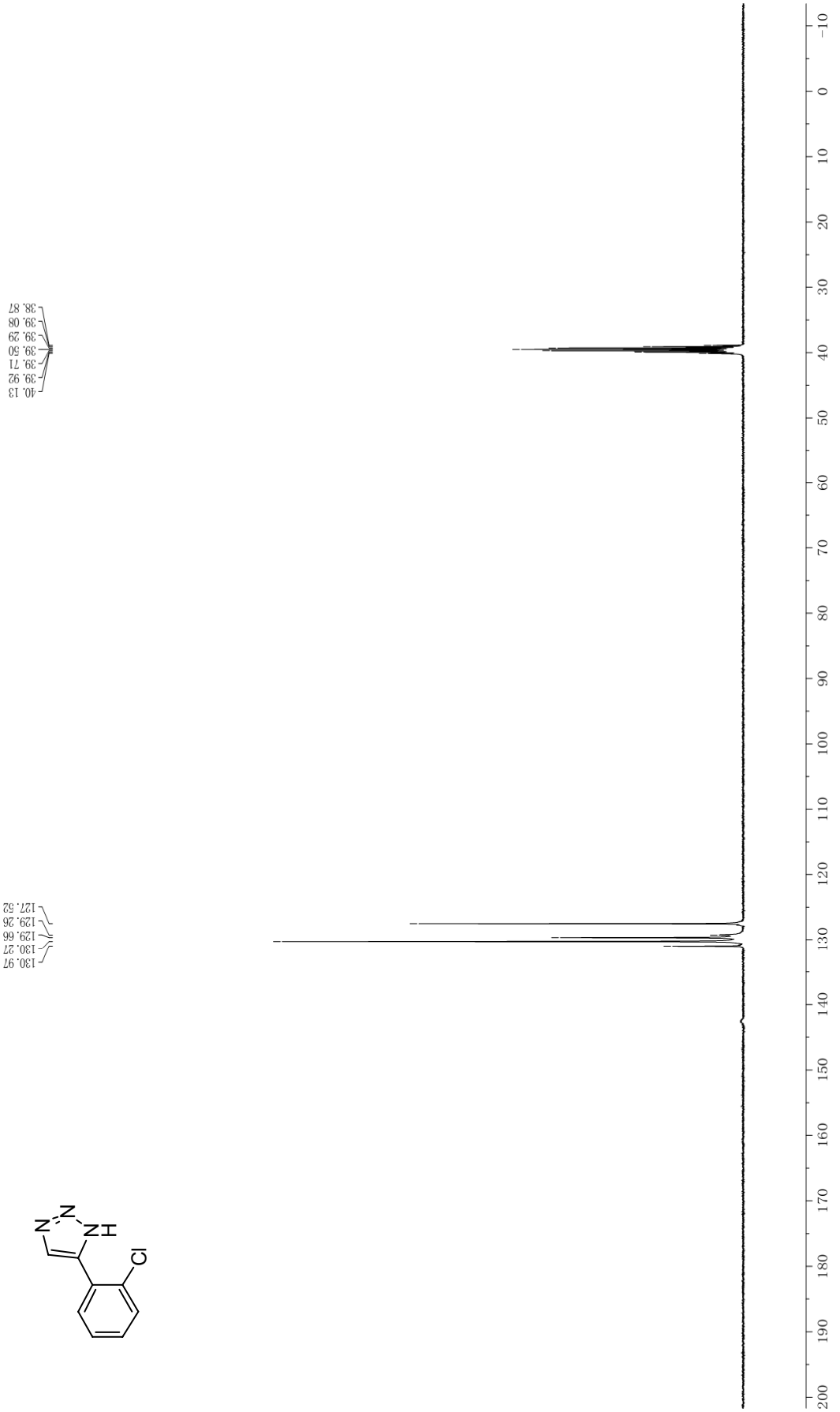


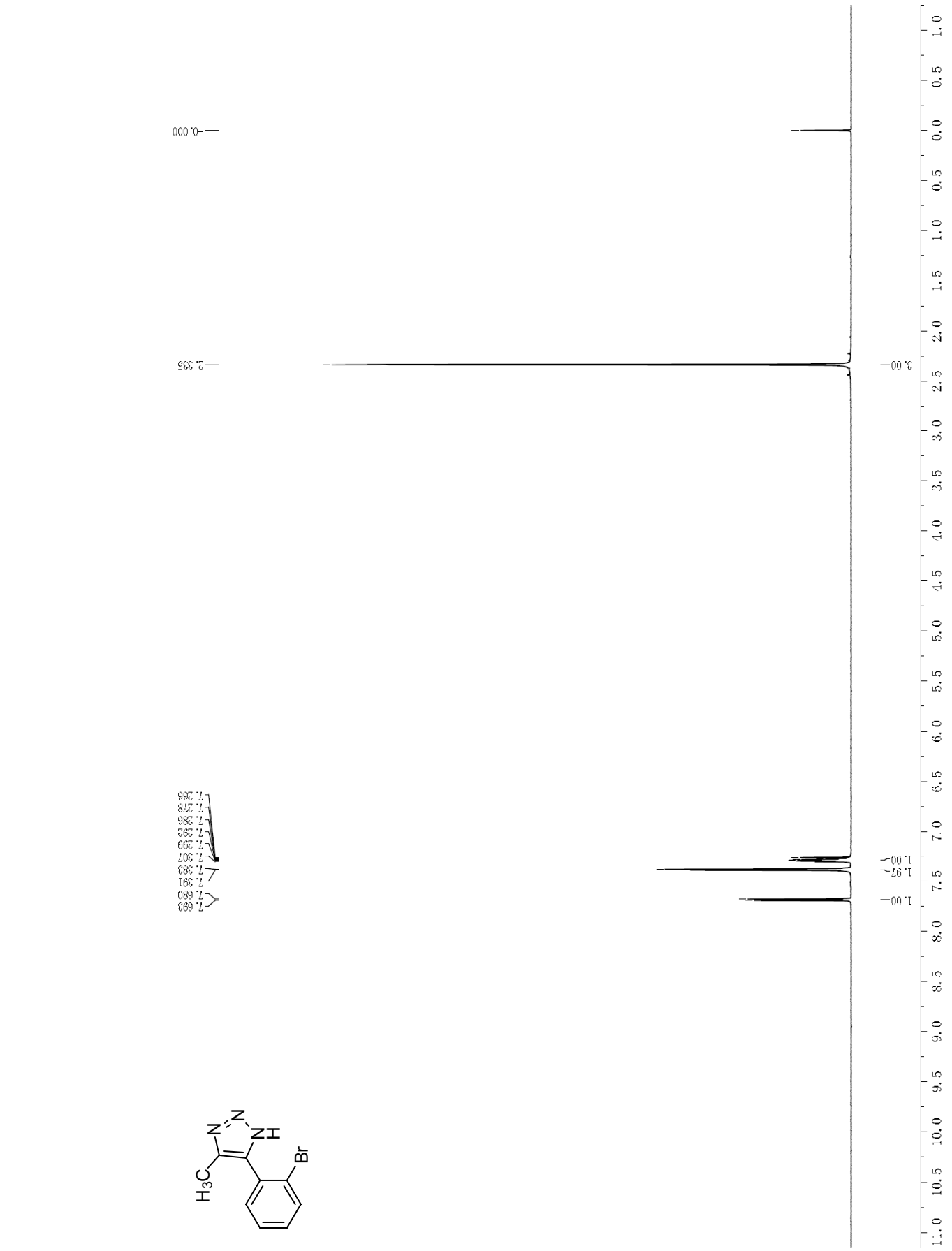
133.57
133.51
130.80
129.90
129.73
127.67
127.54
121.75

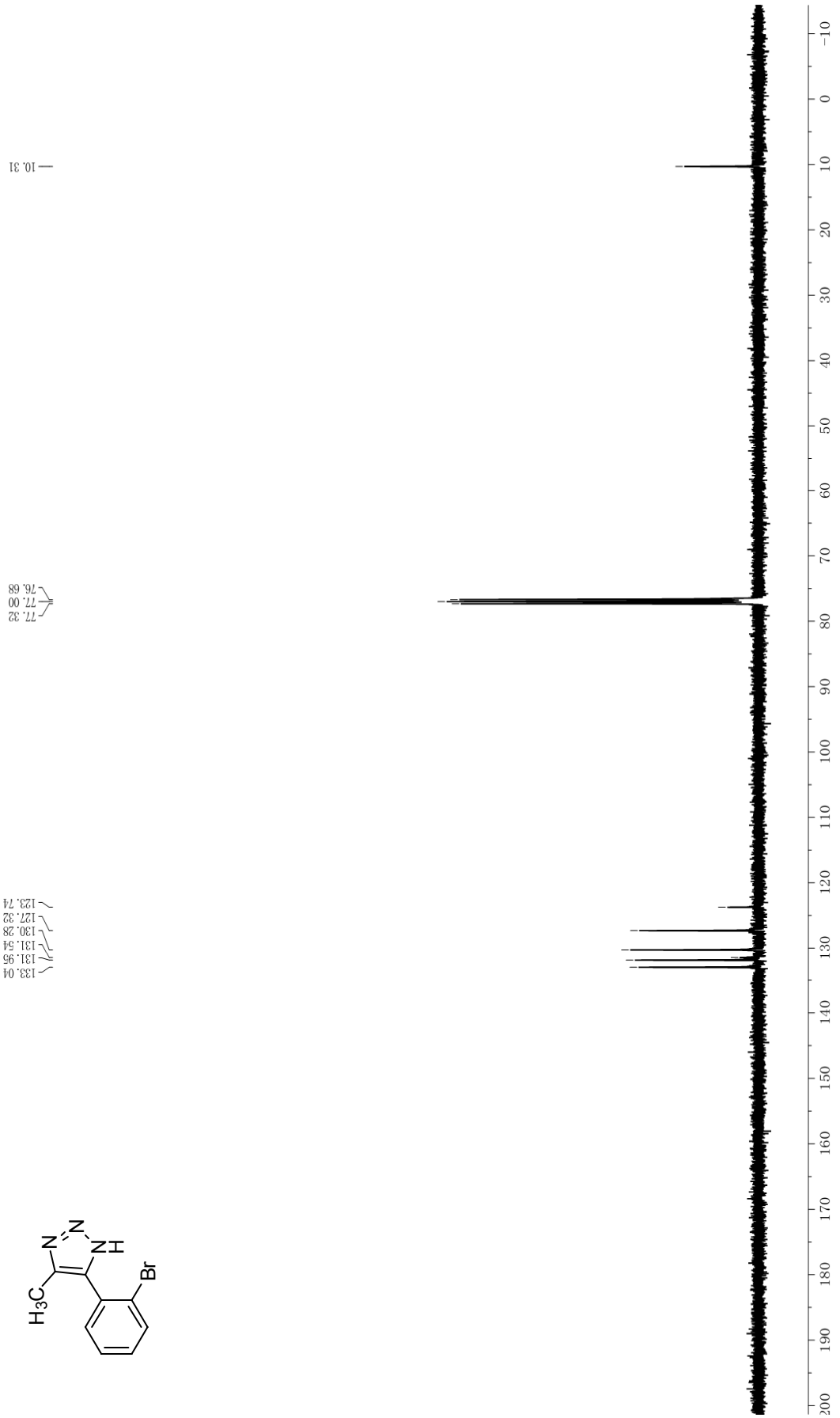
77.22
77.00
76.79

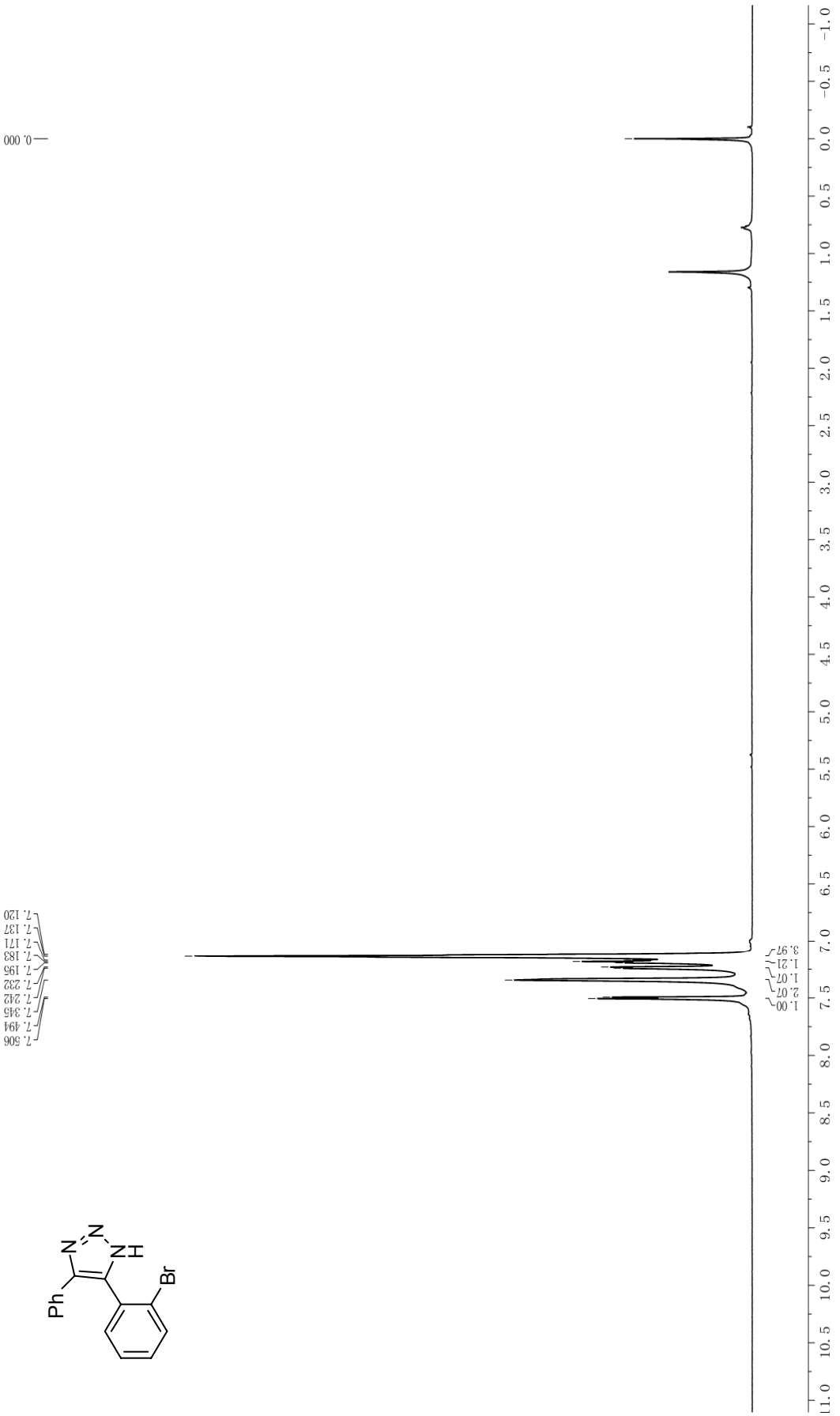


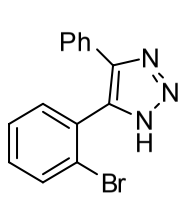












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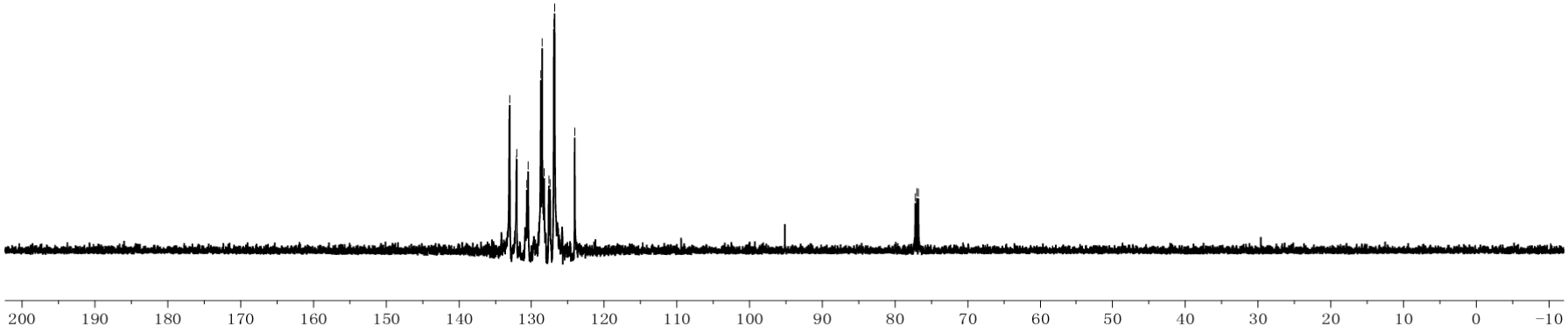
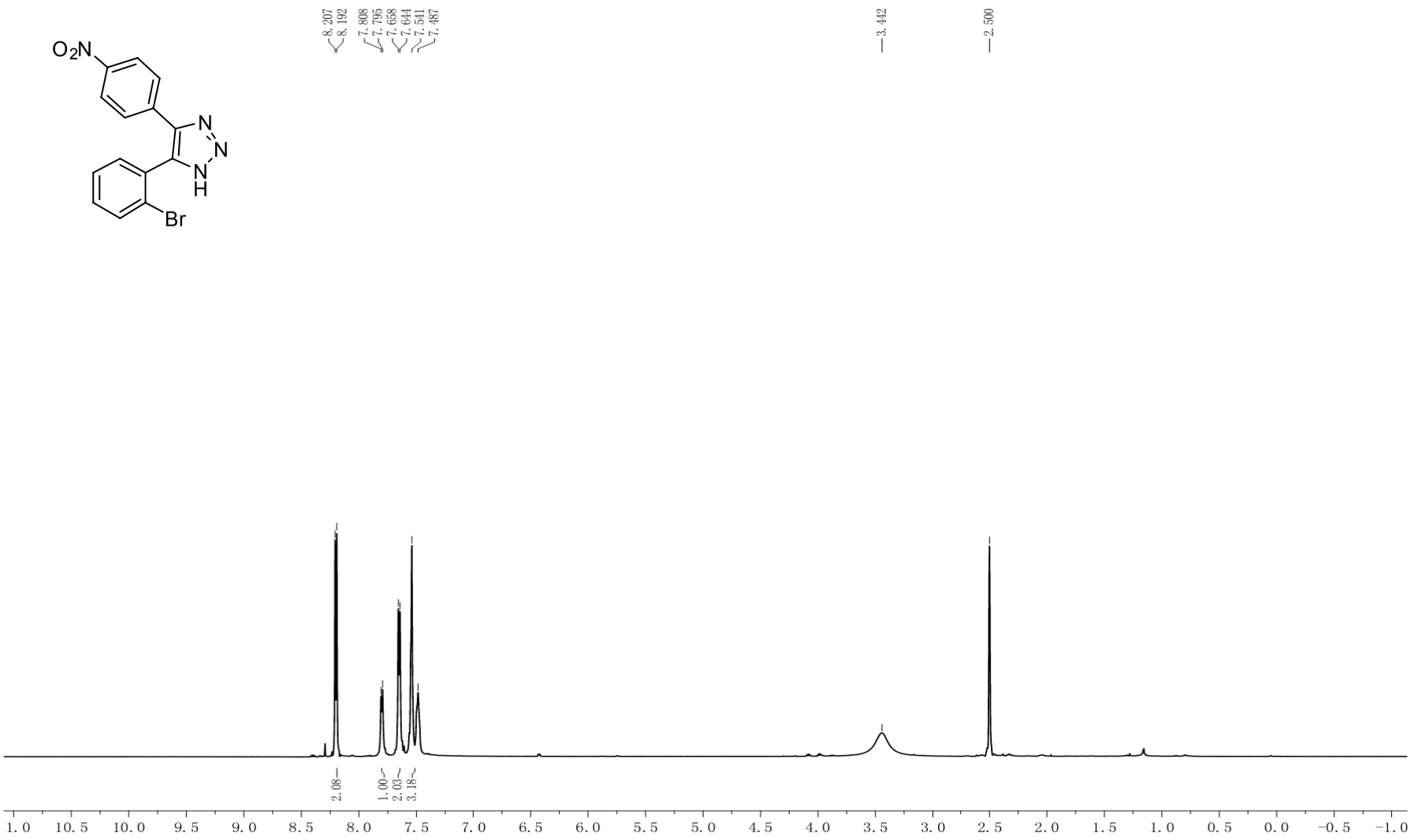
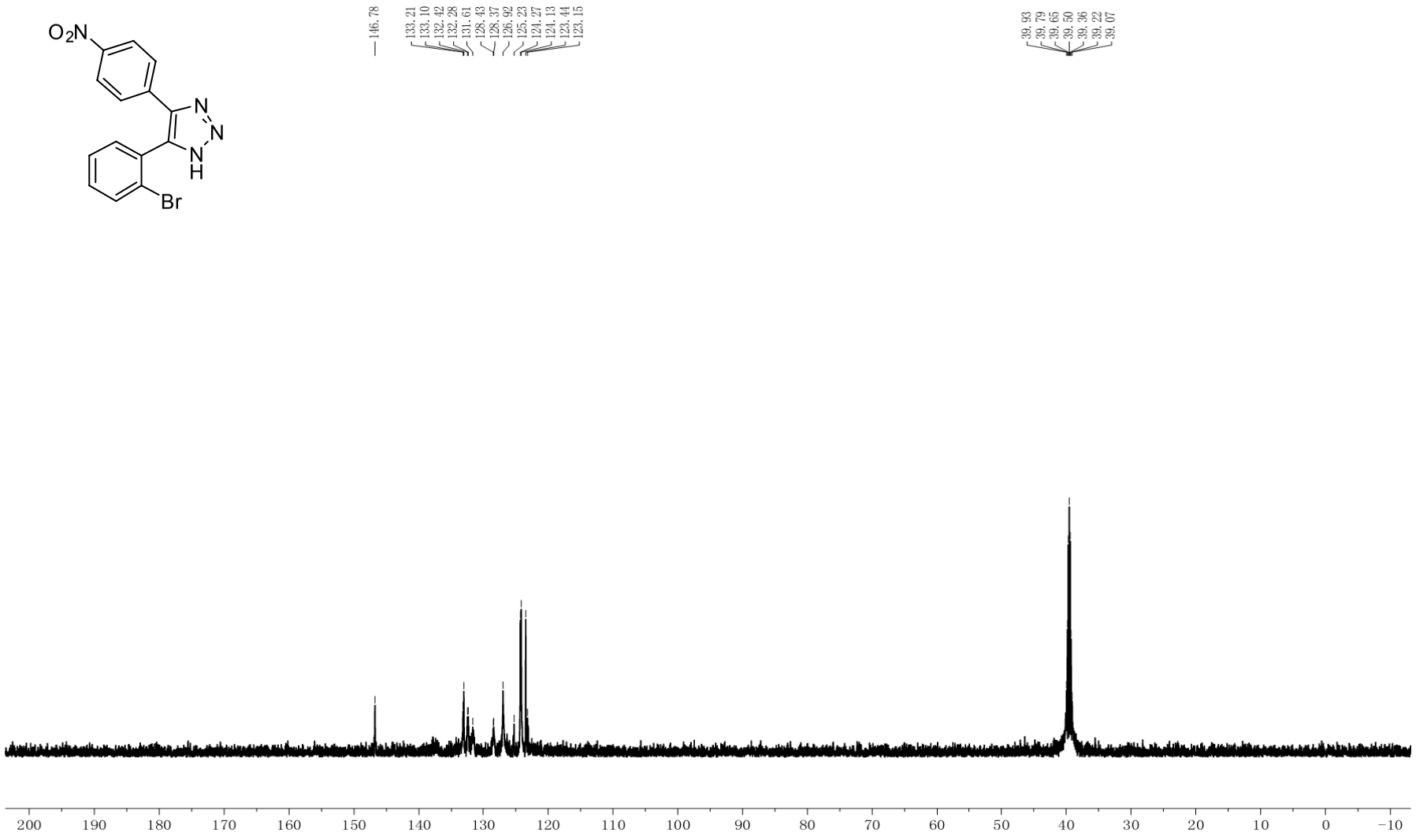
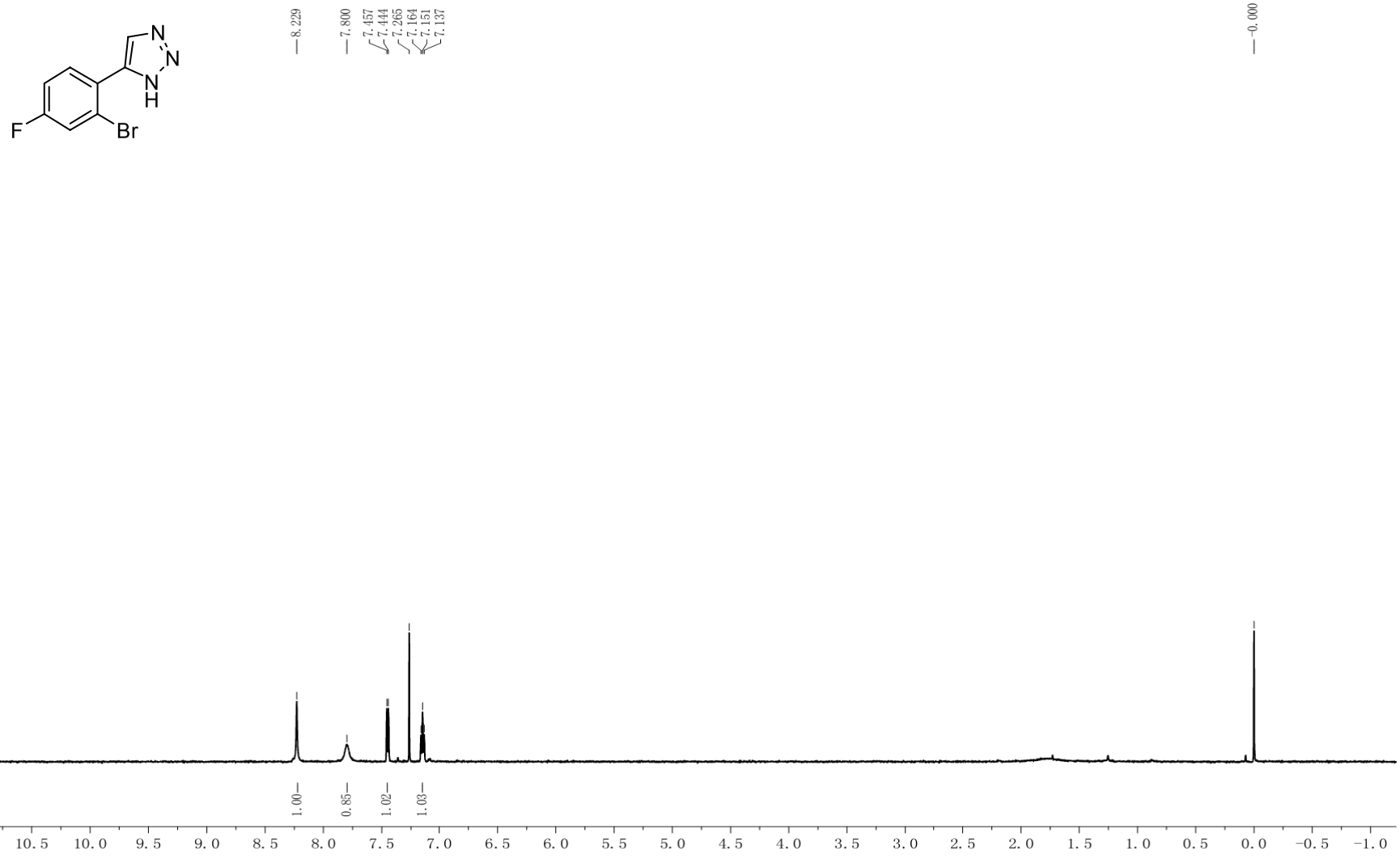
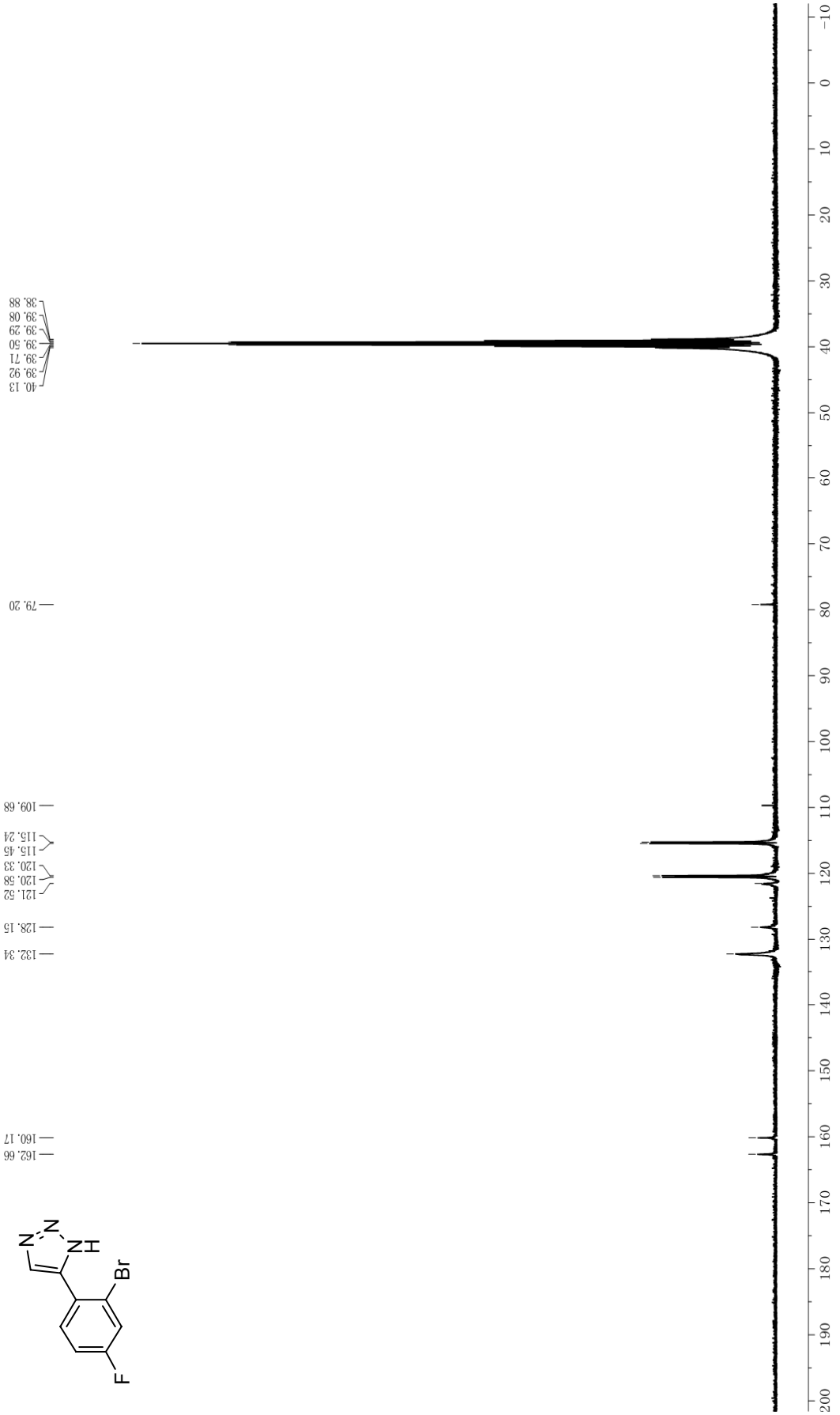
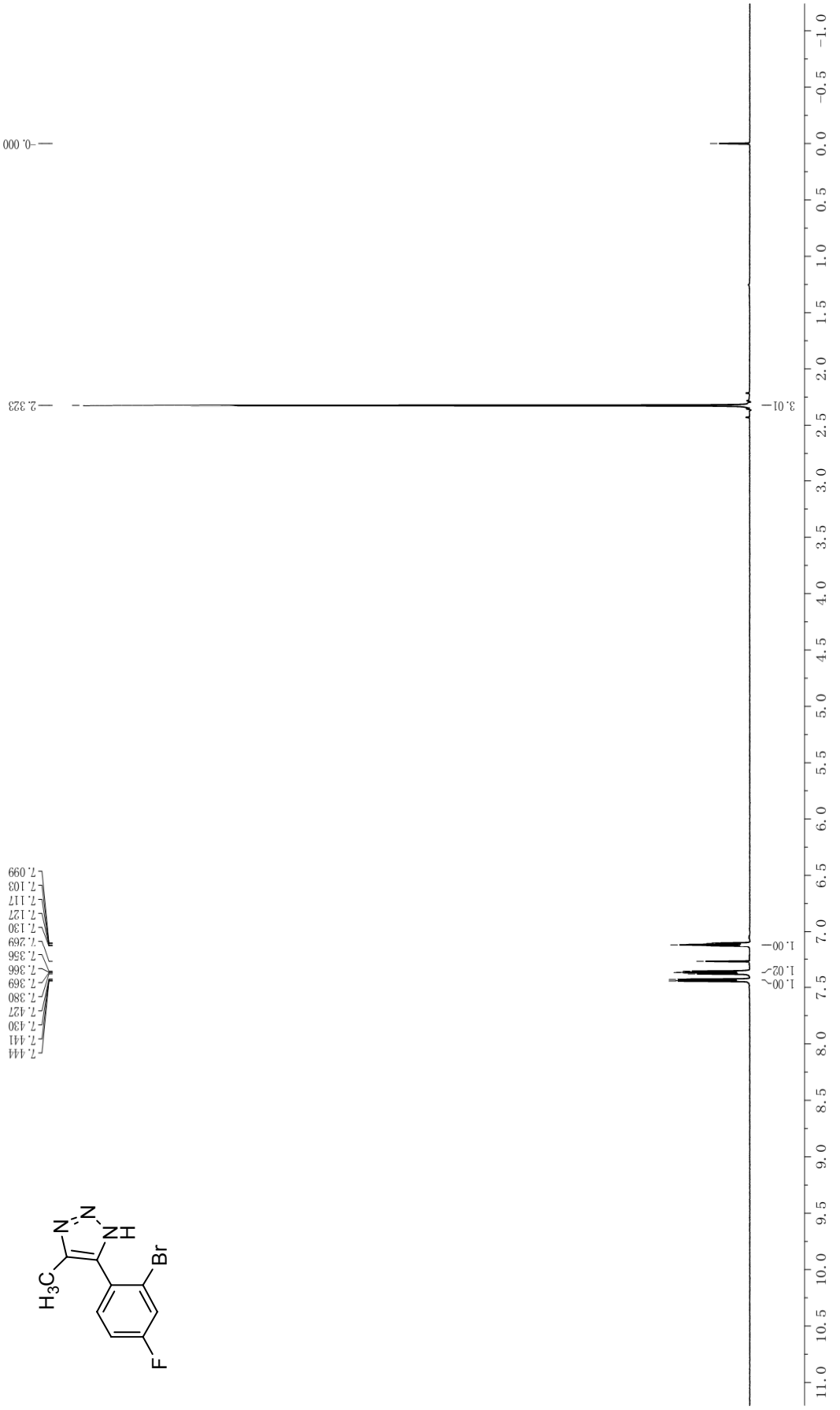


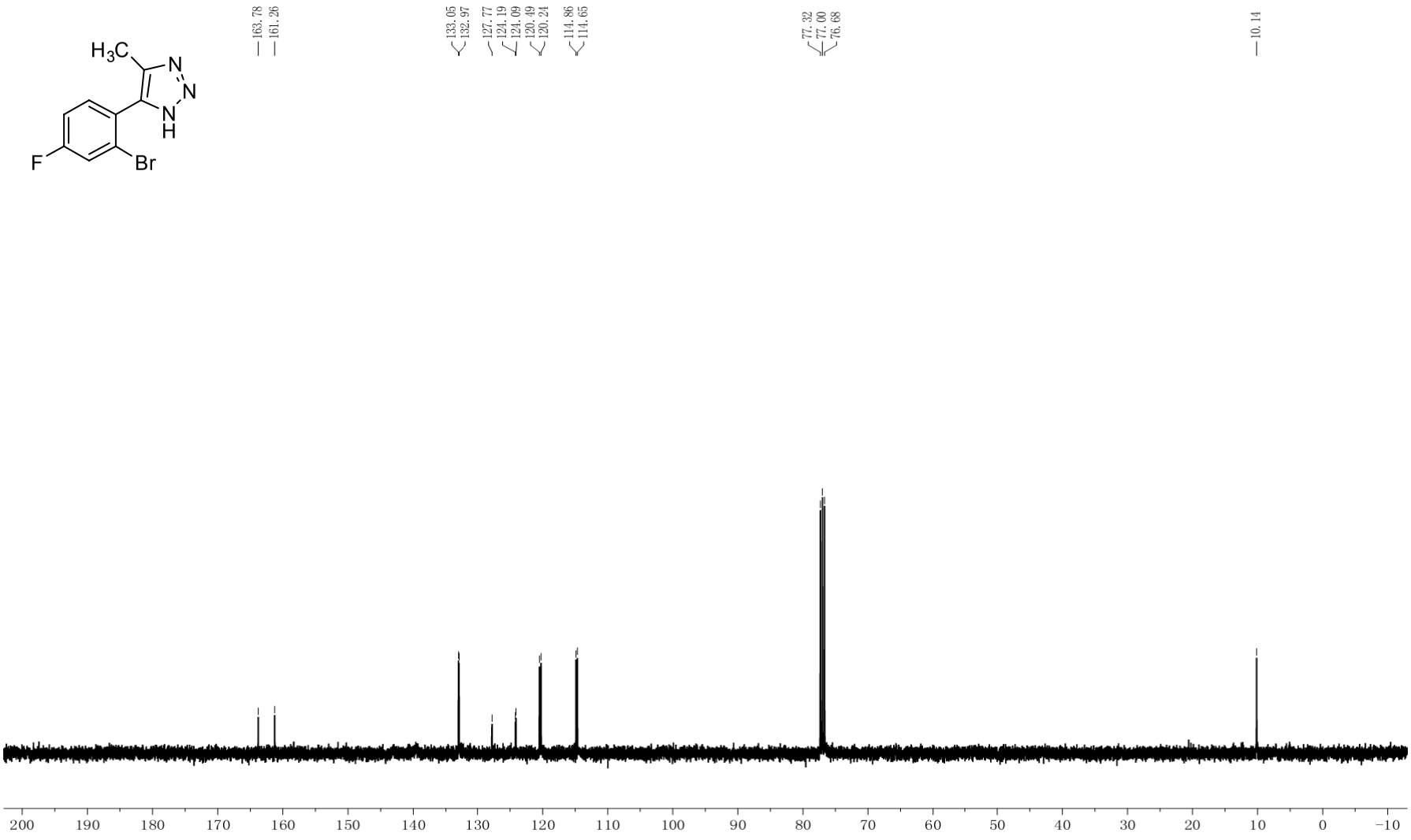


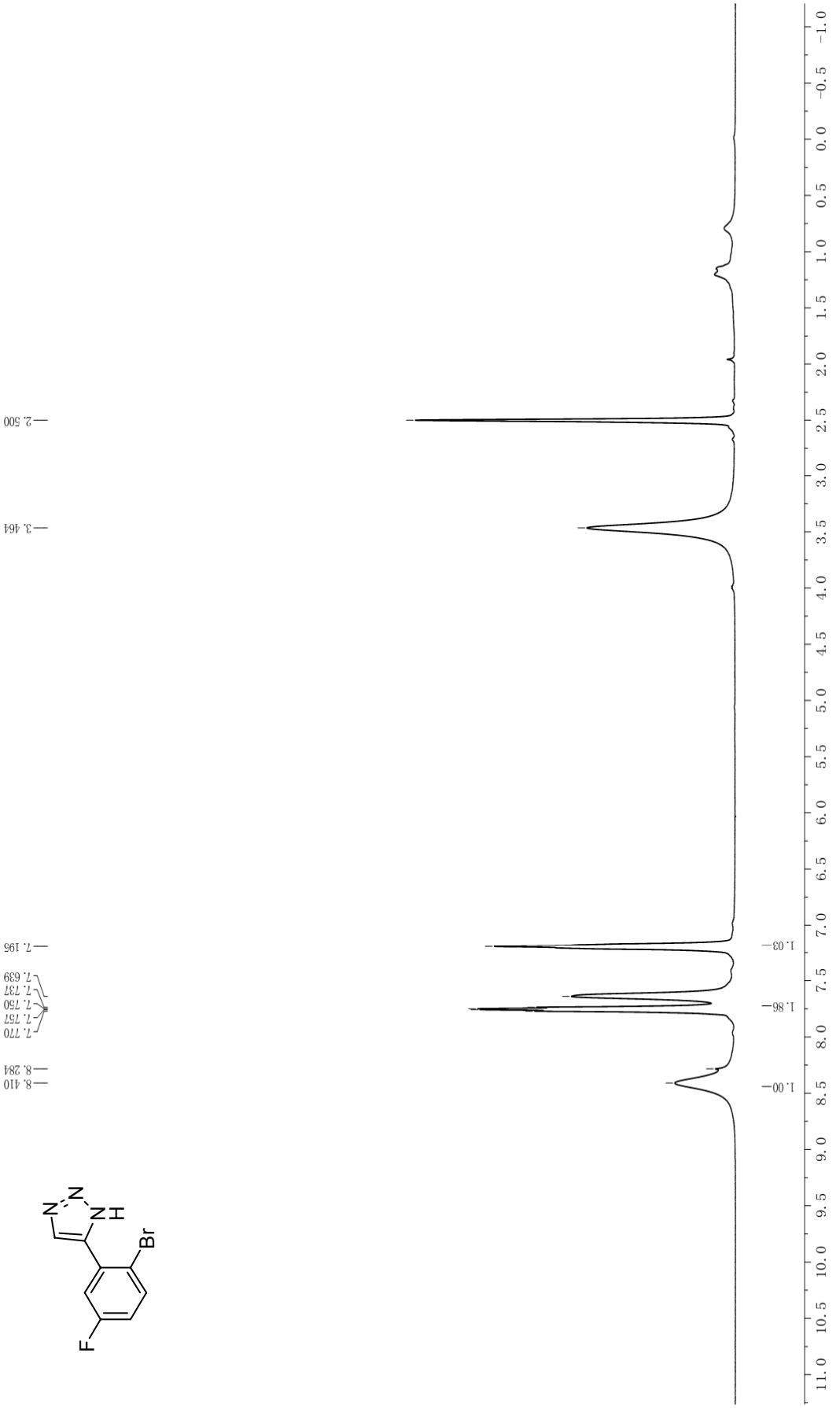


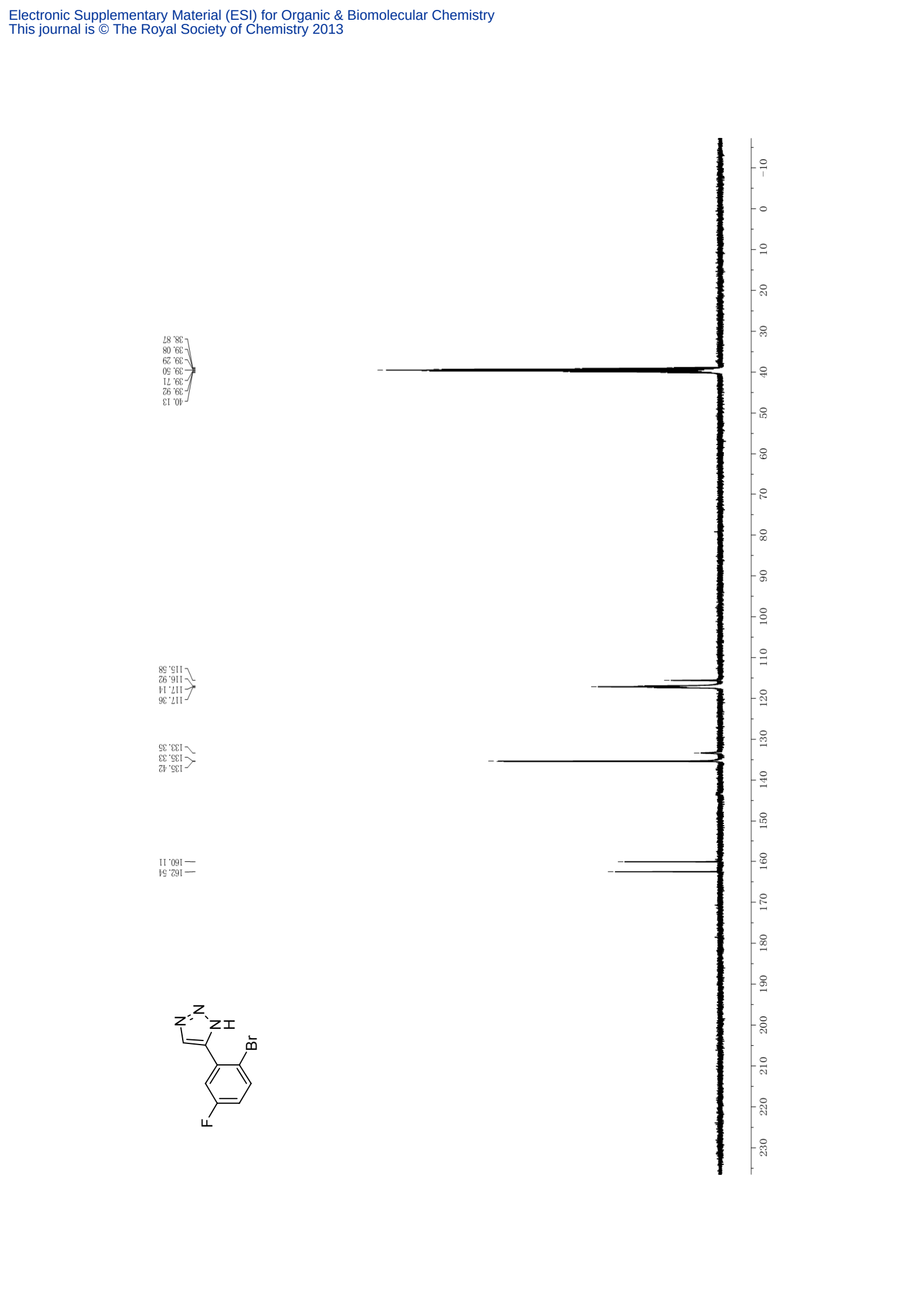


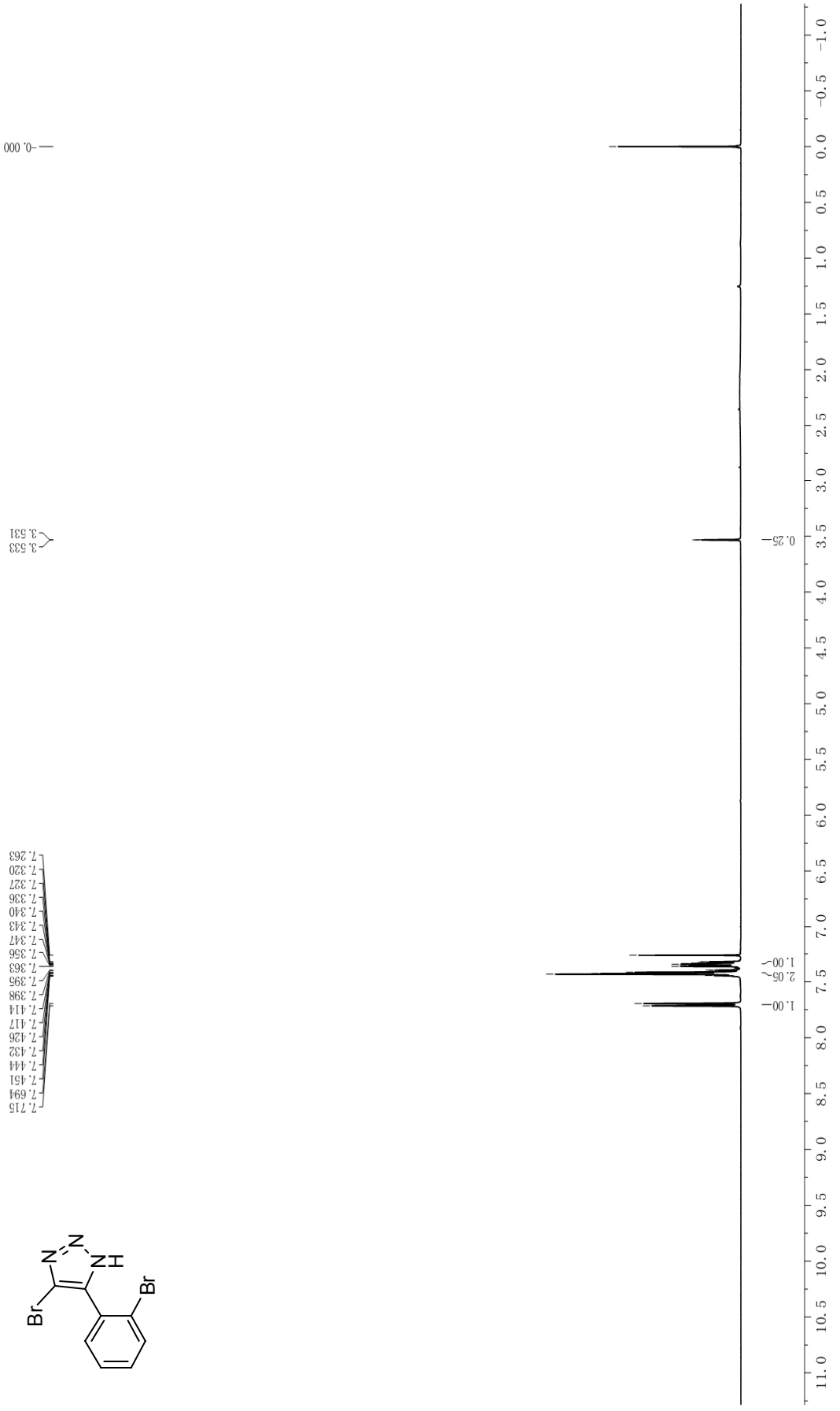


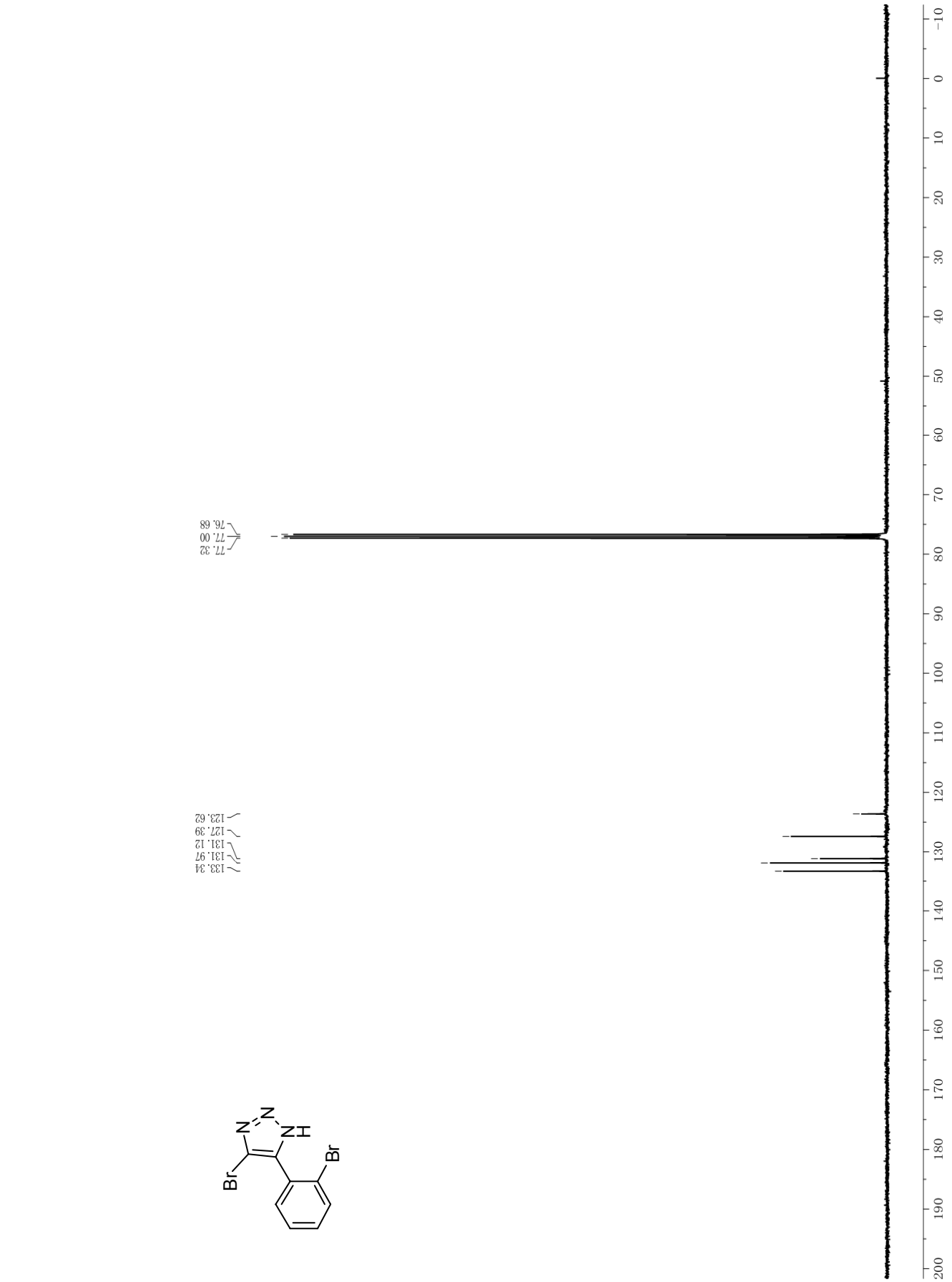


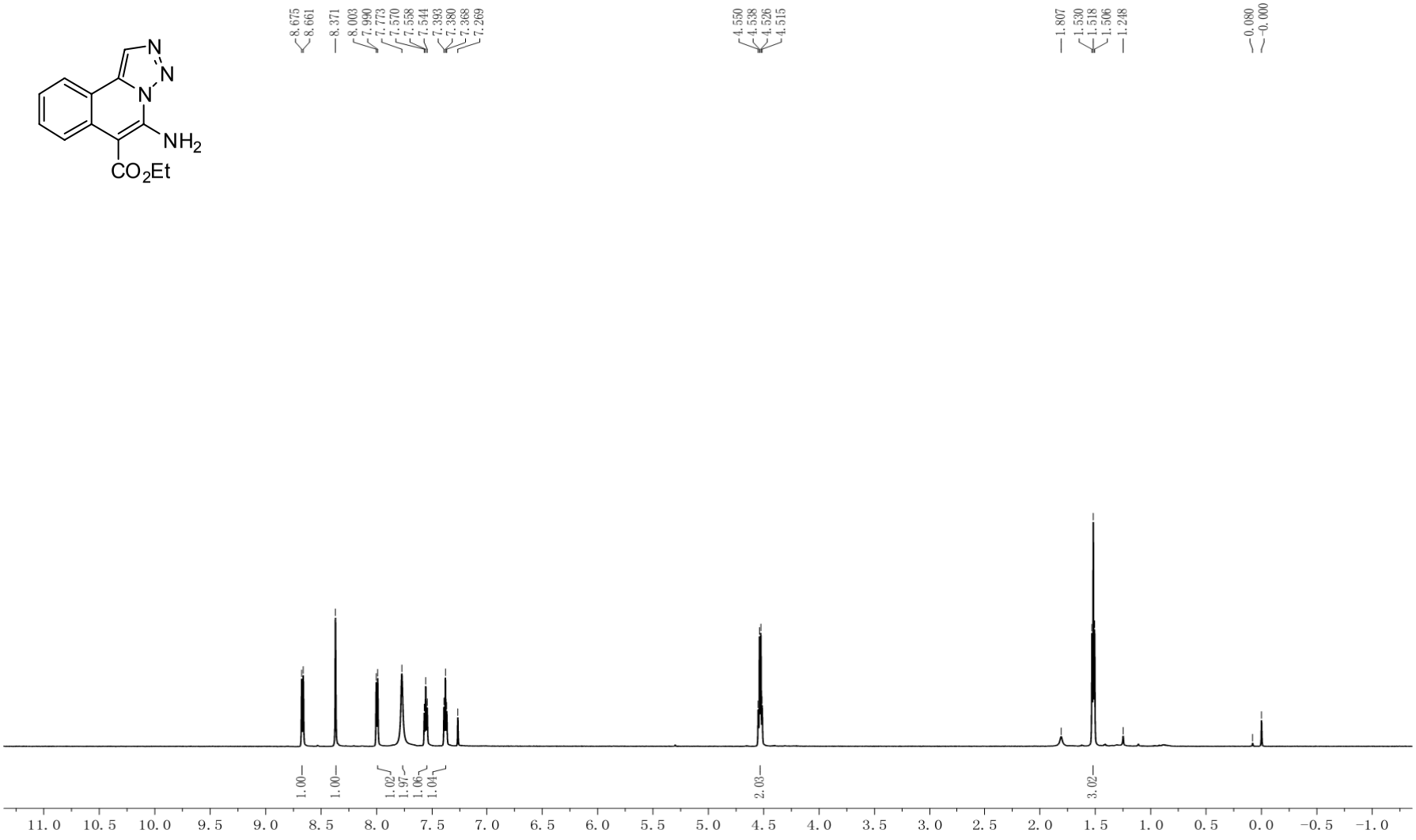


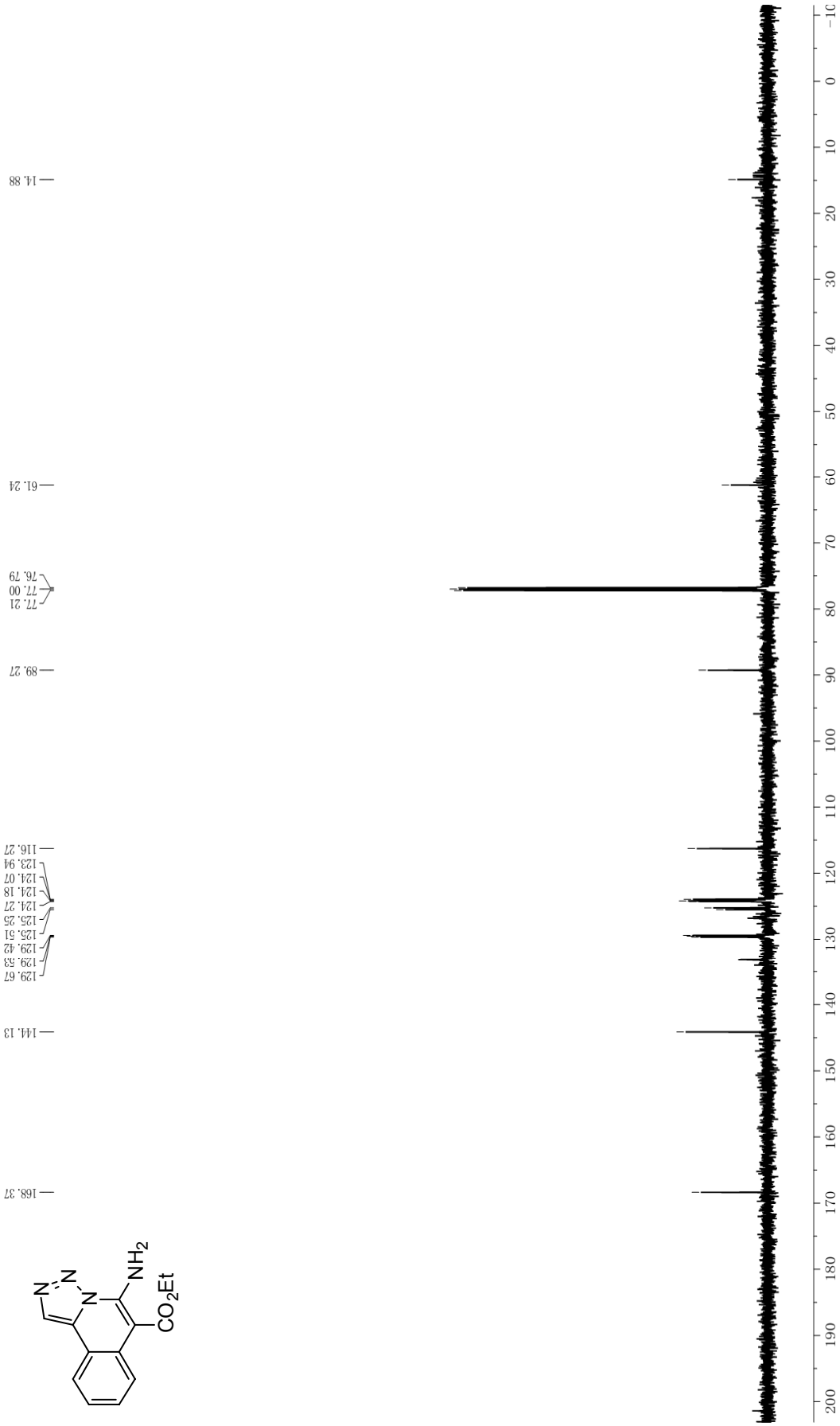


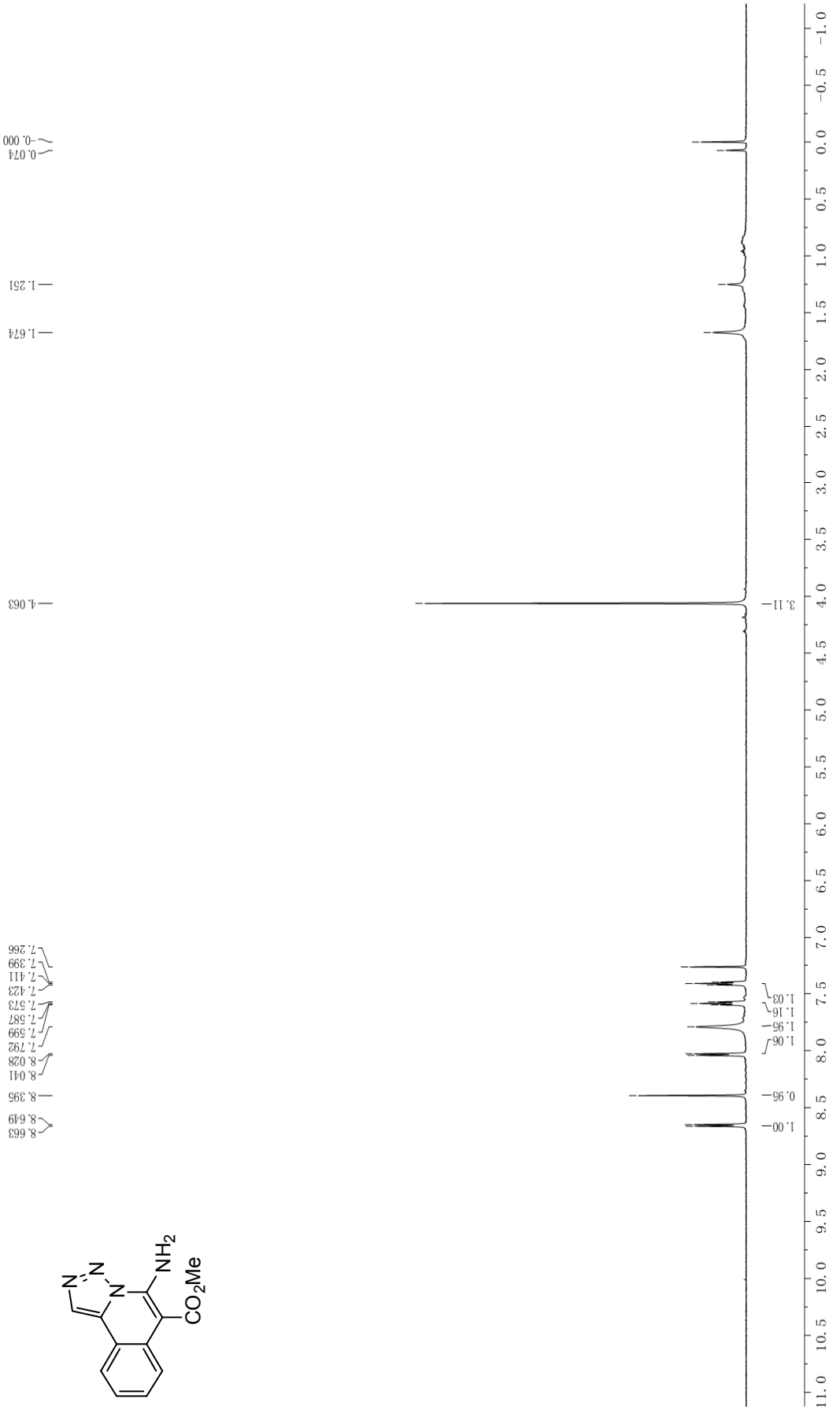


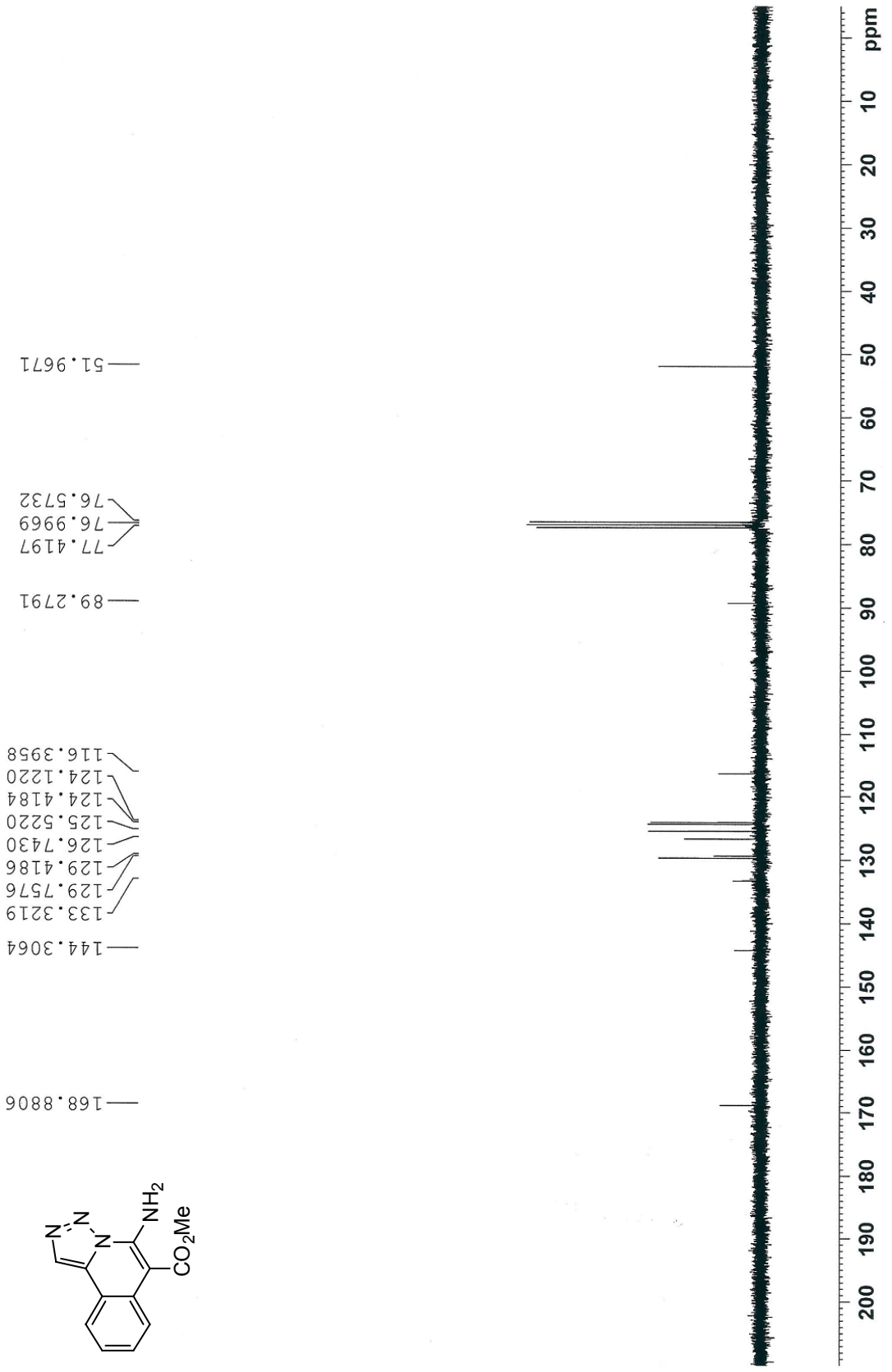


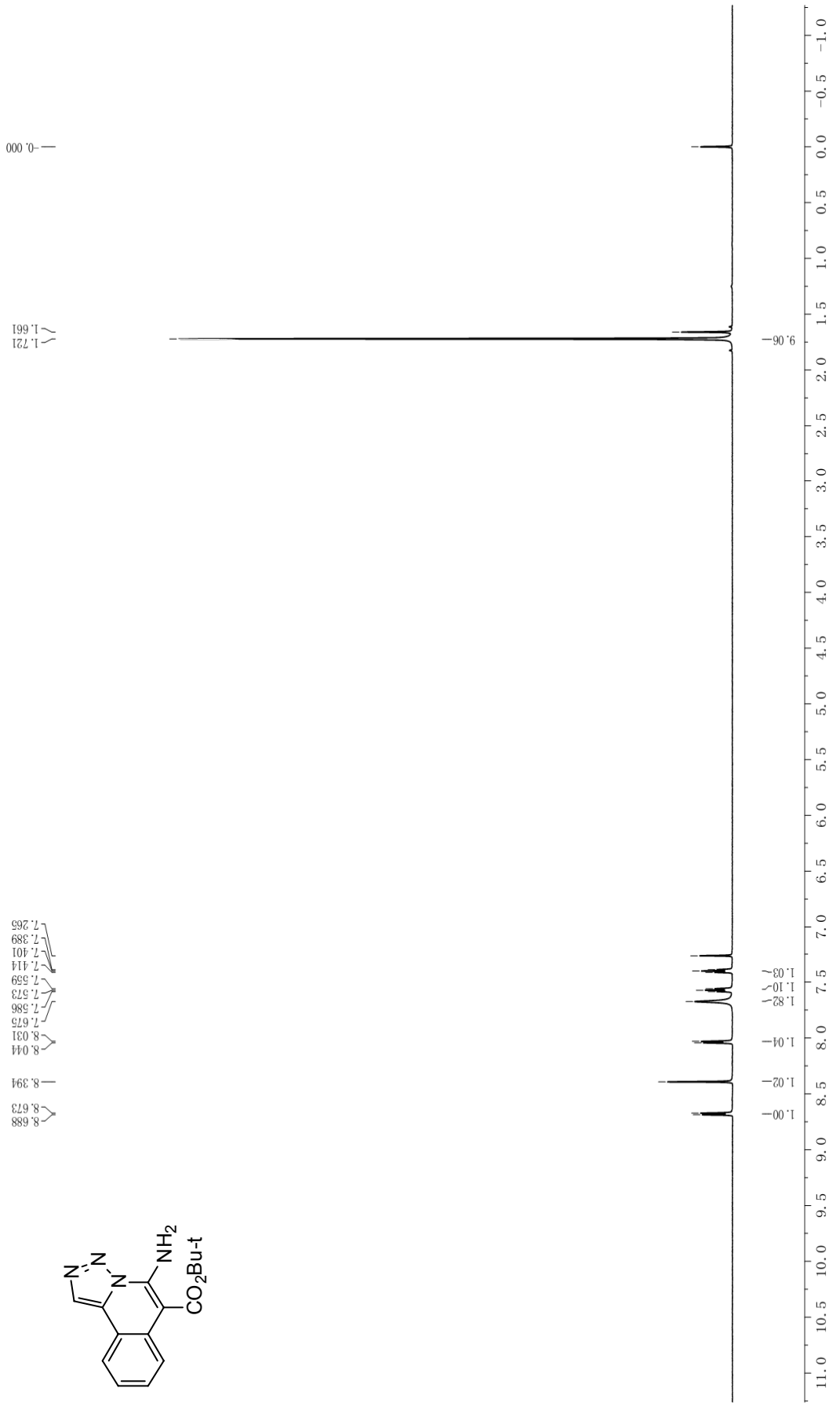


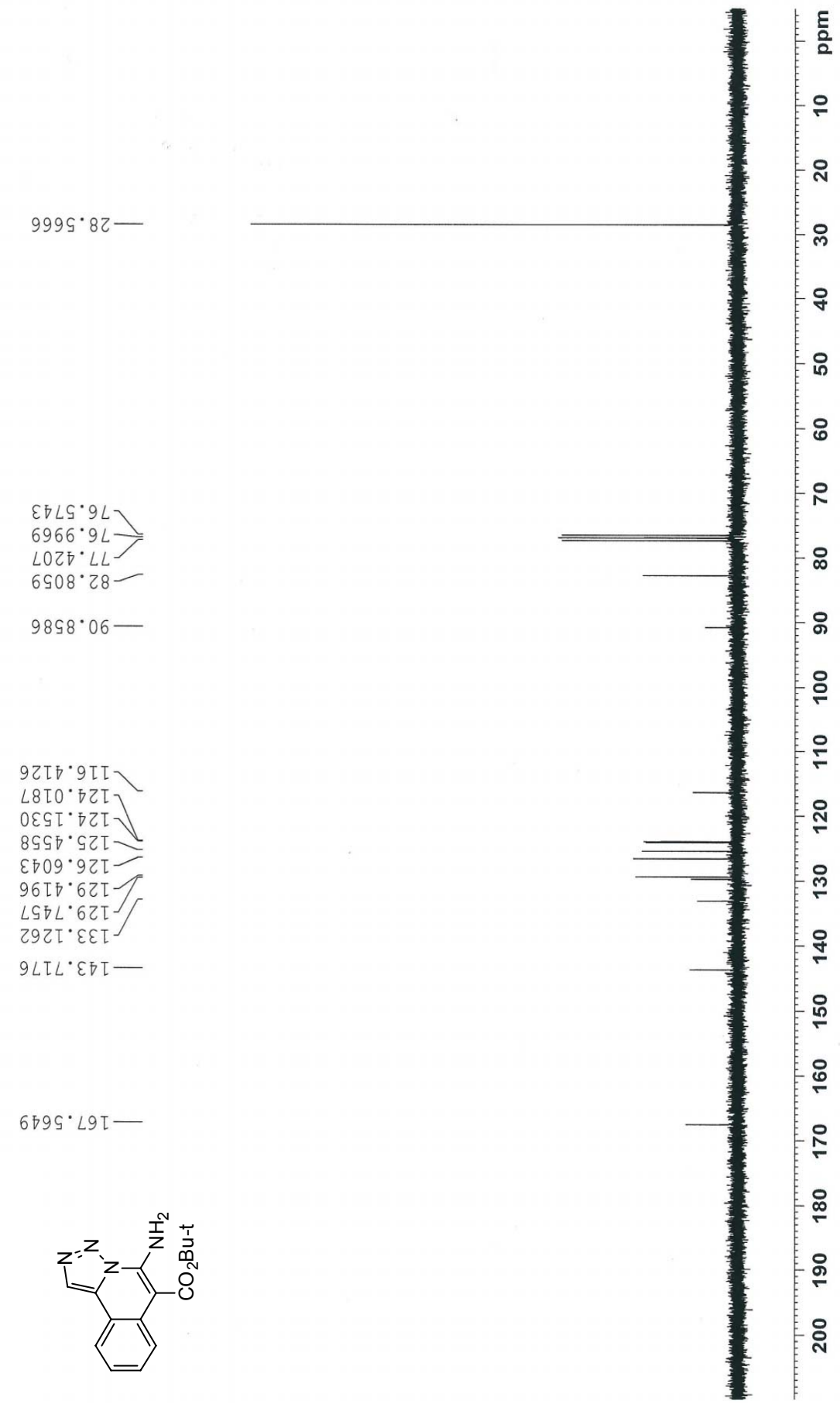


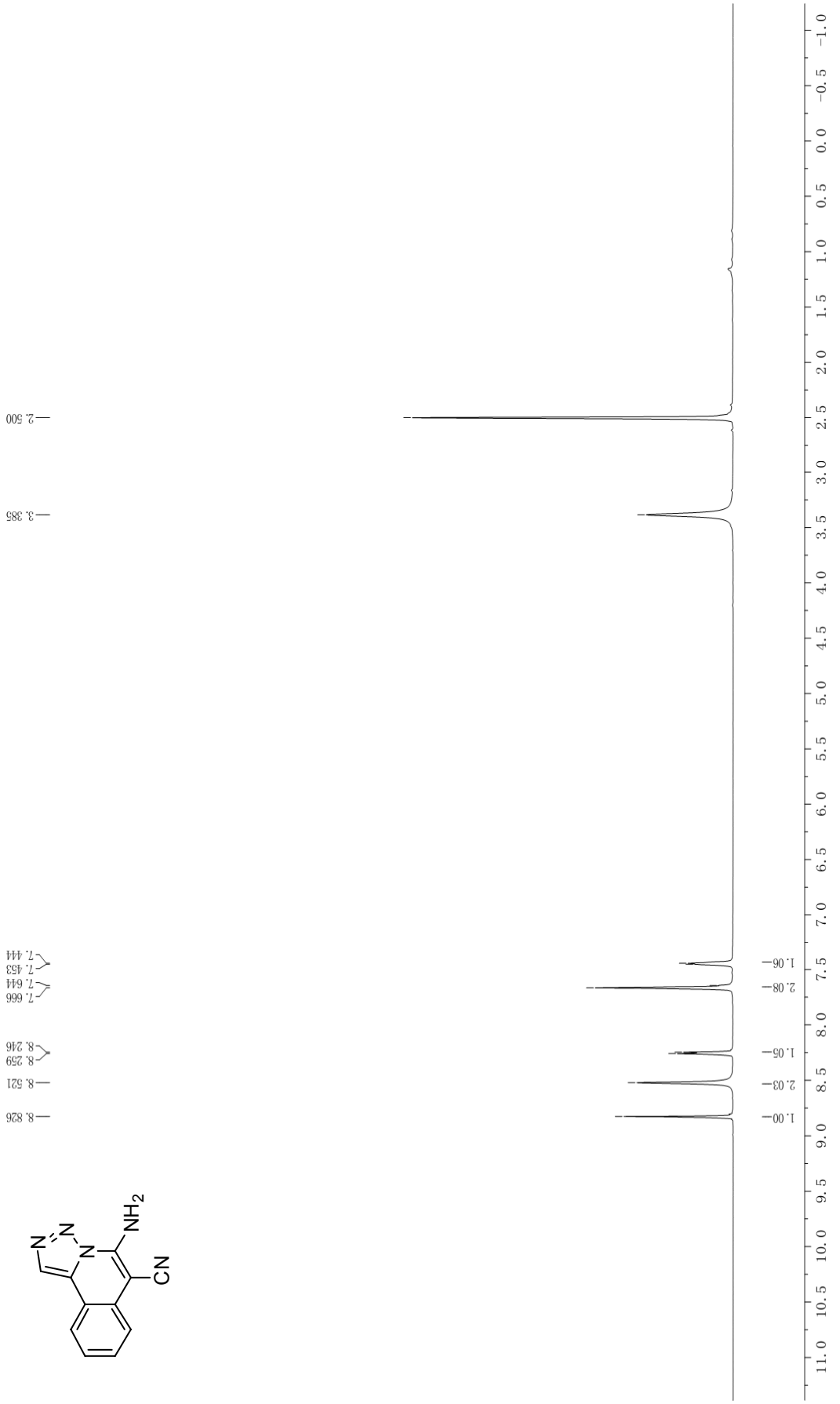


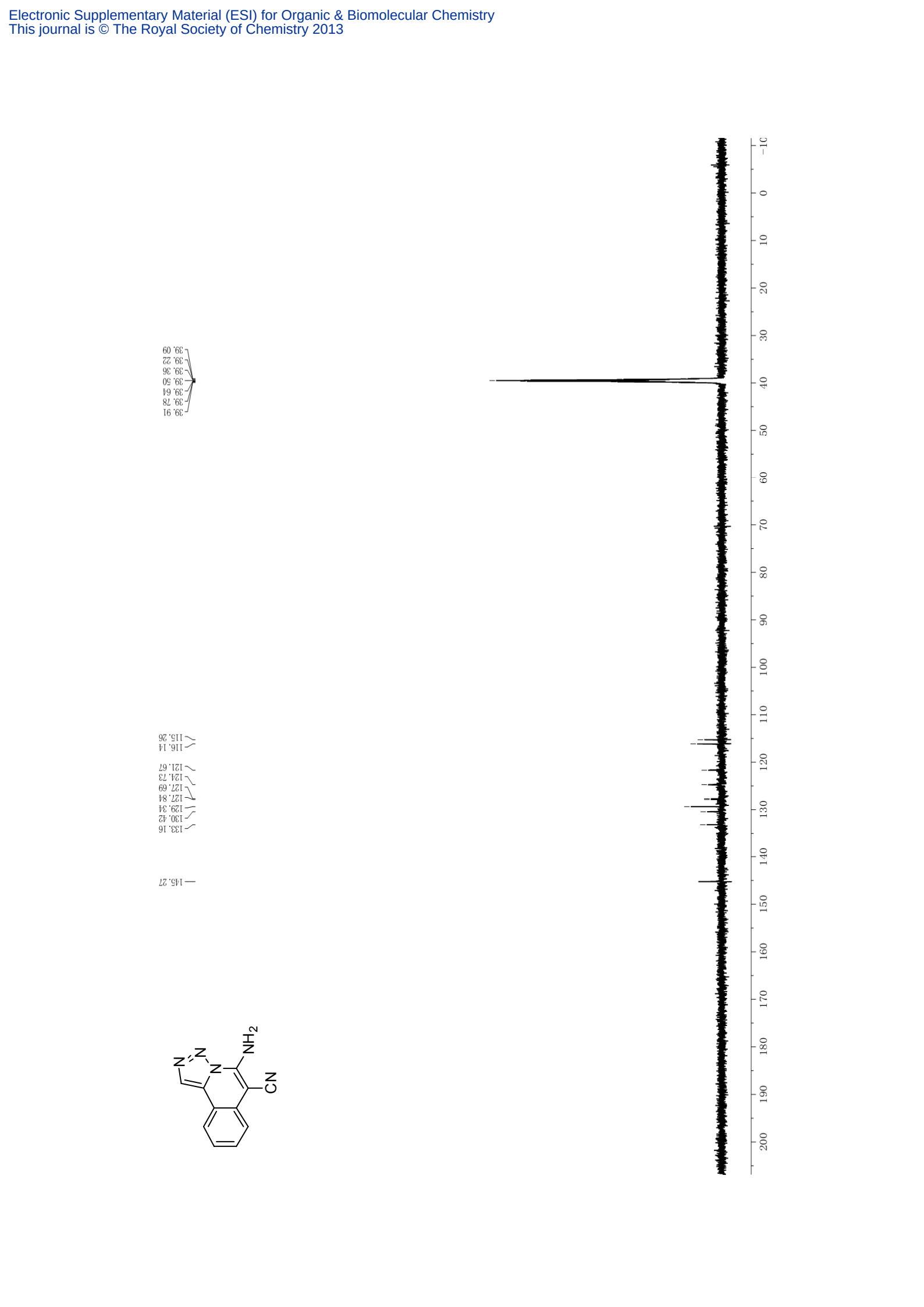


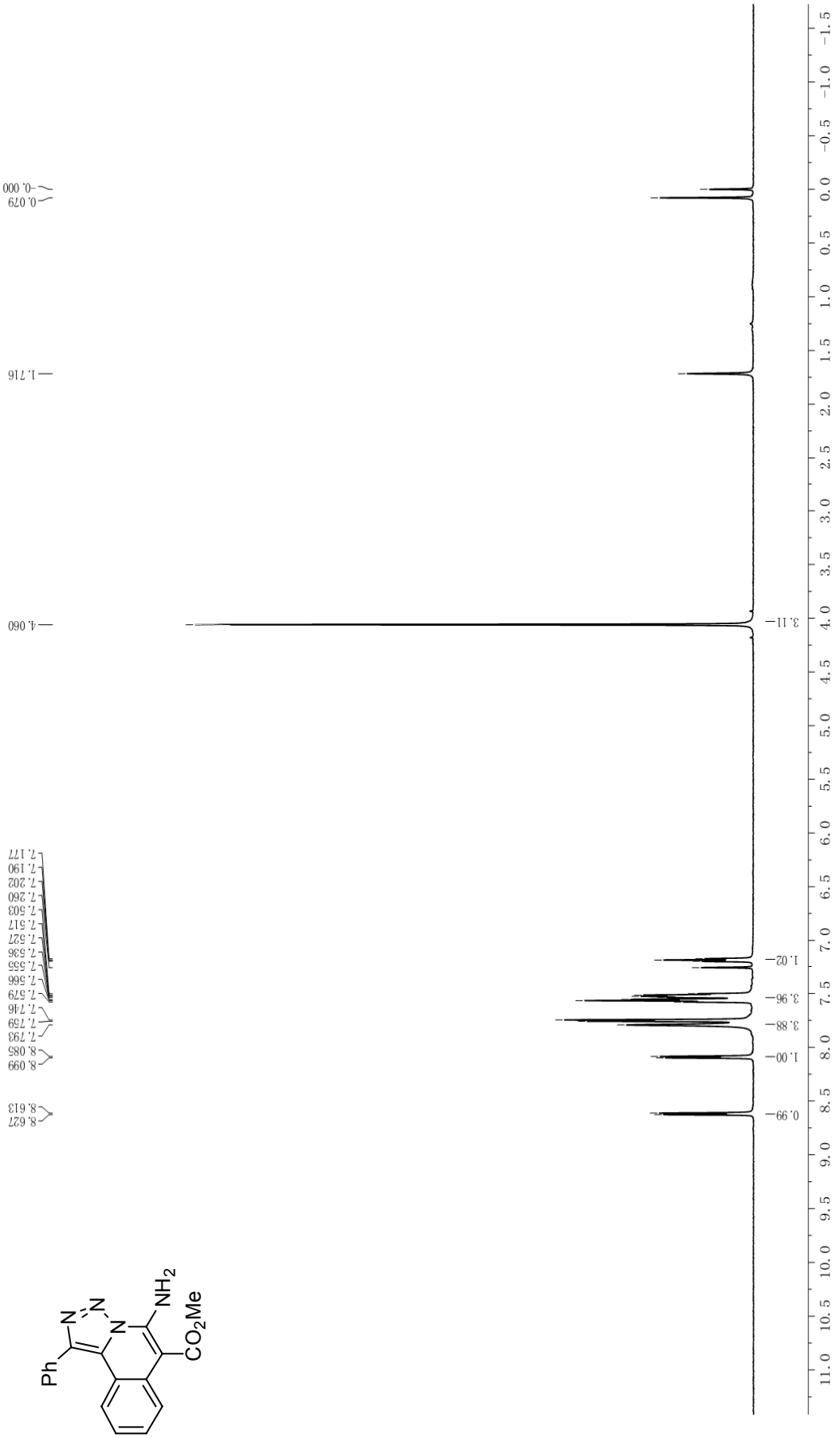


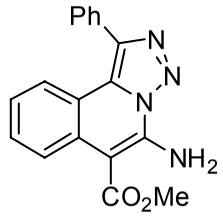


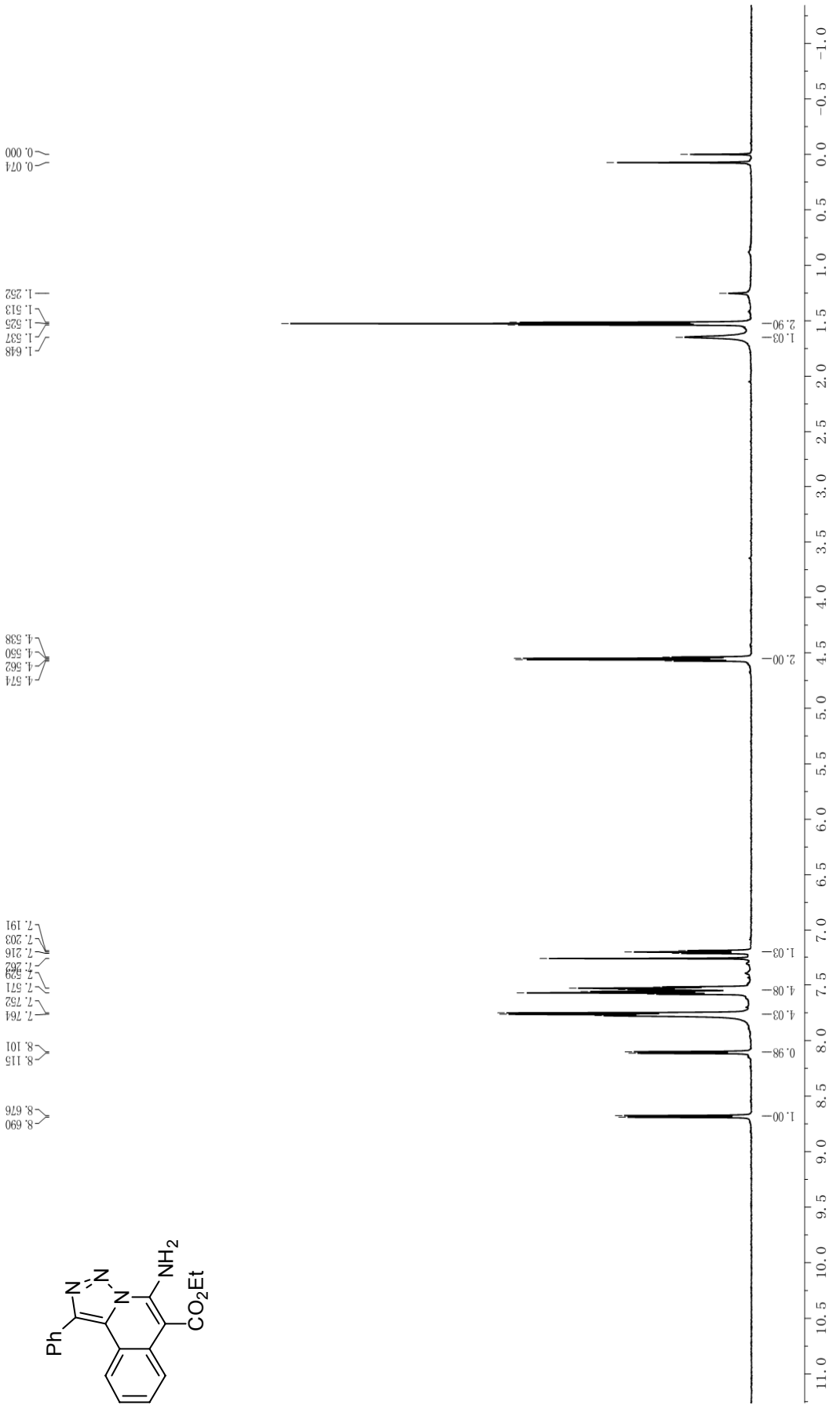


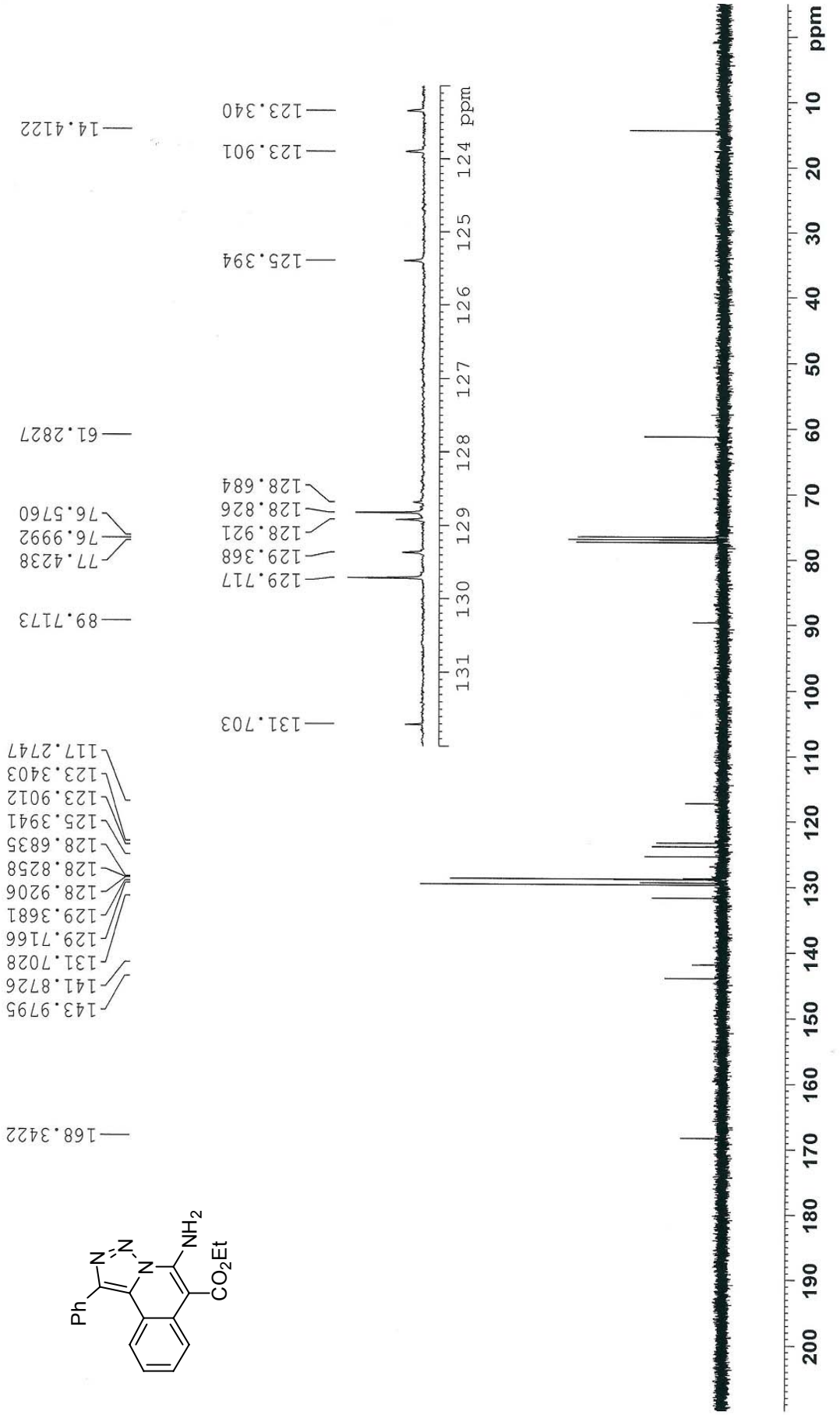


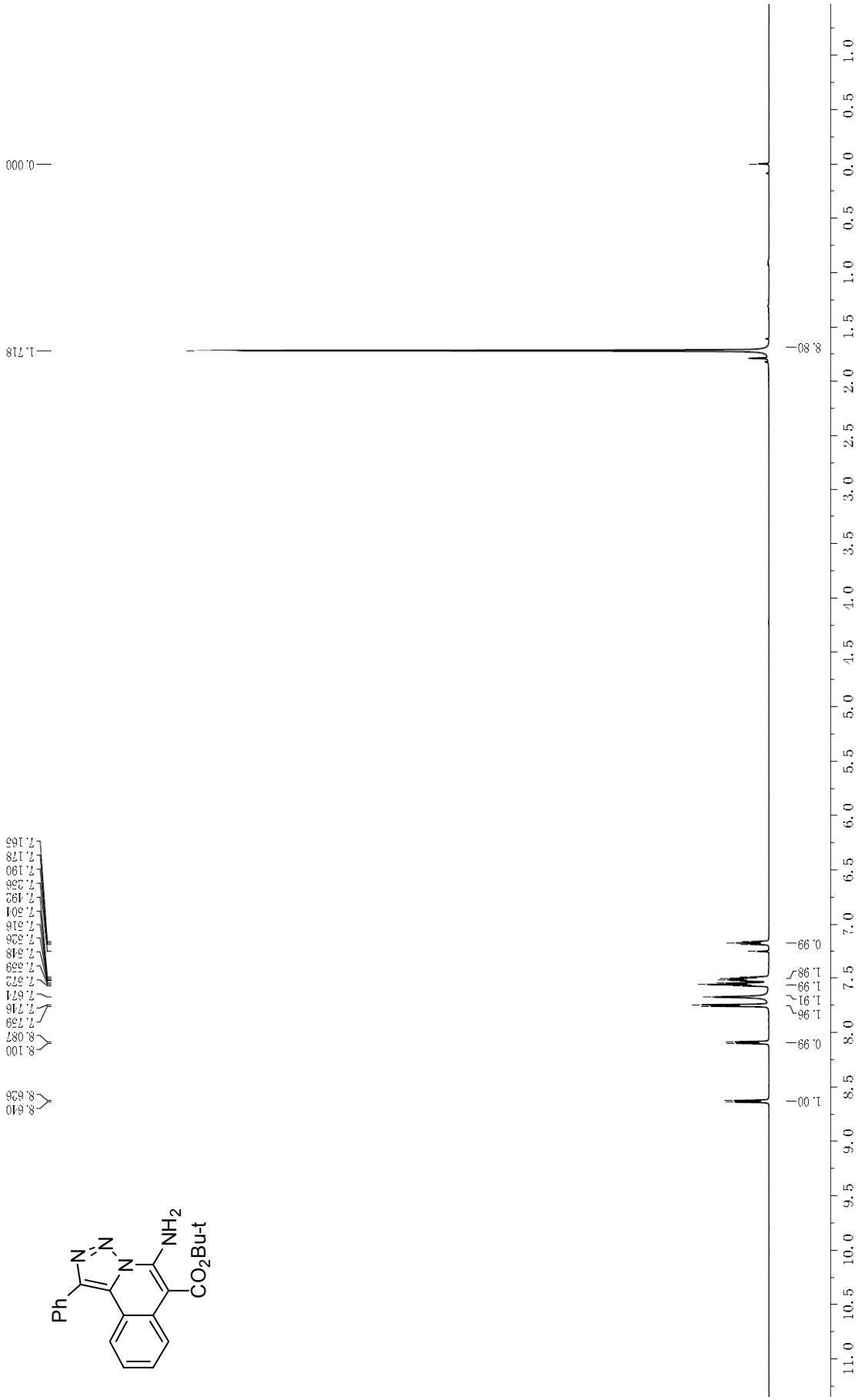


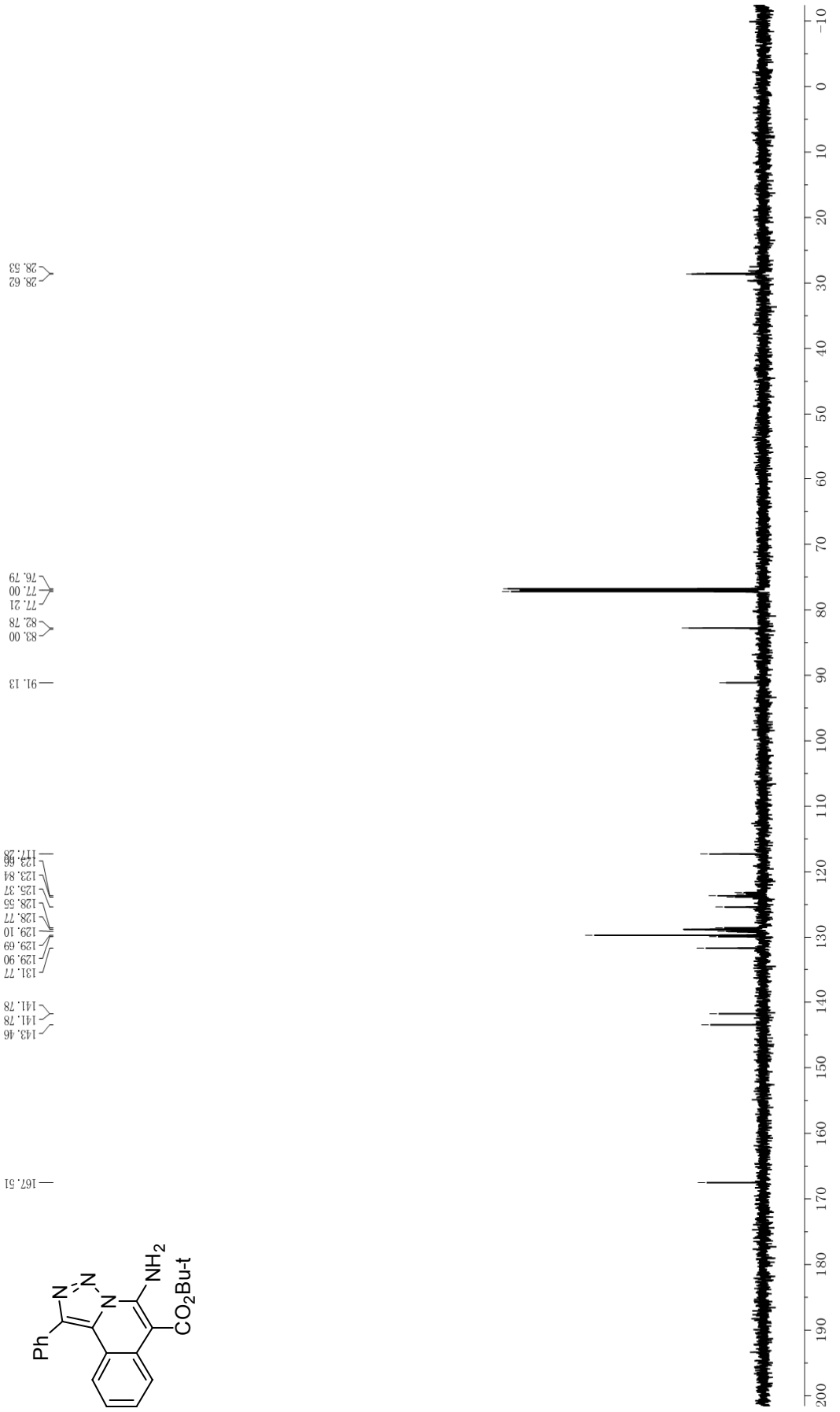


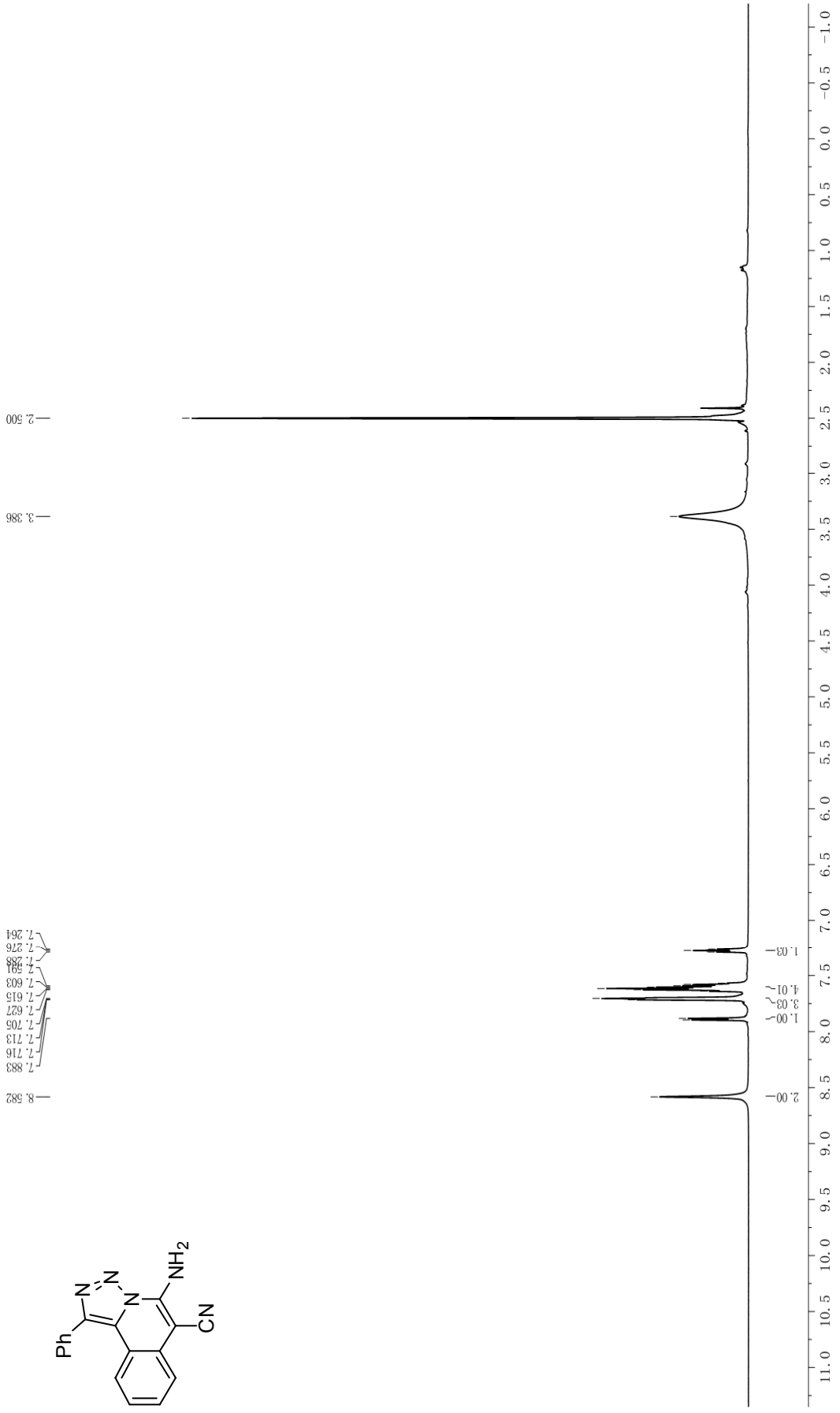


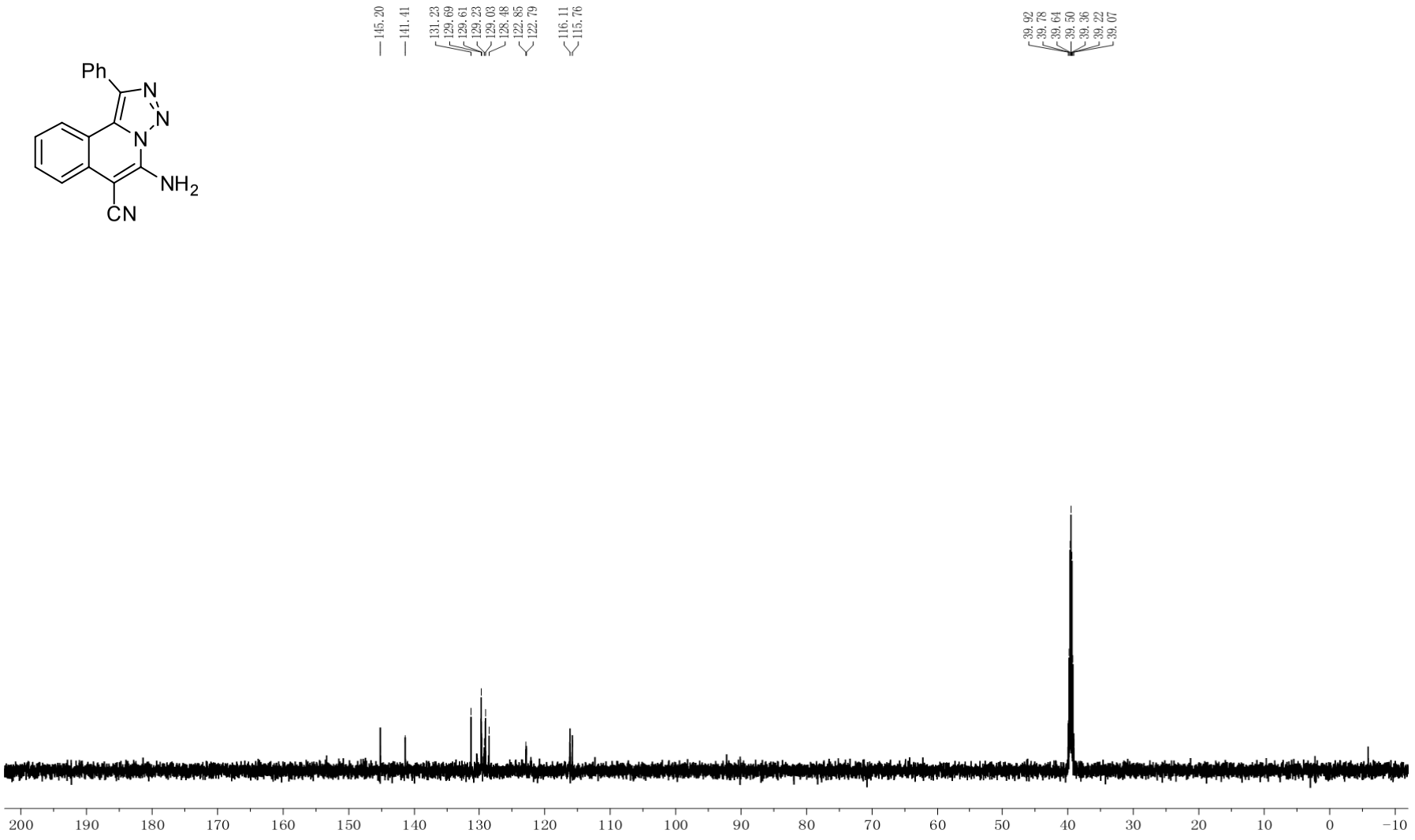


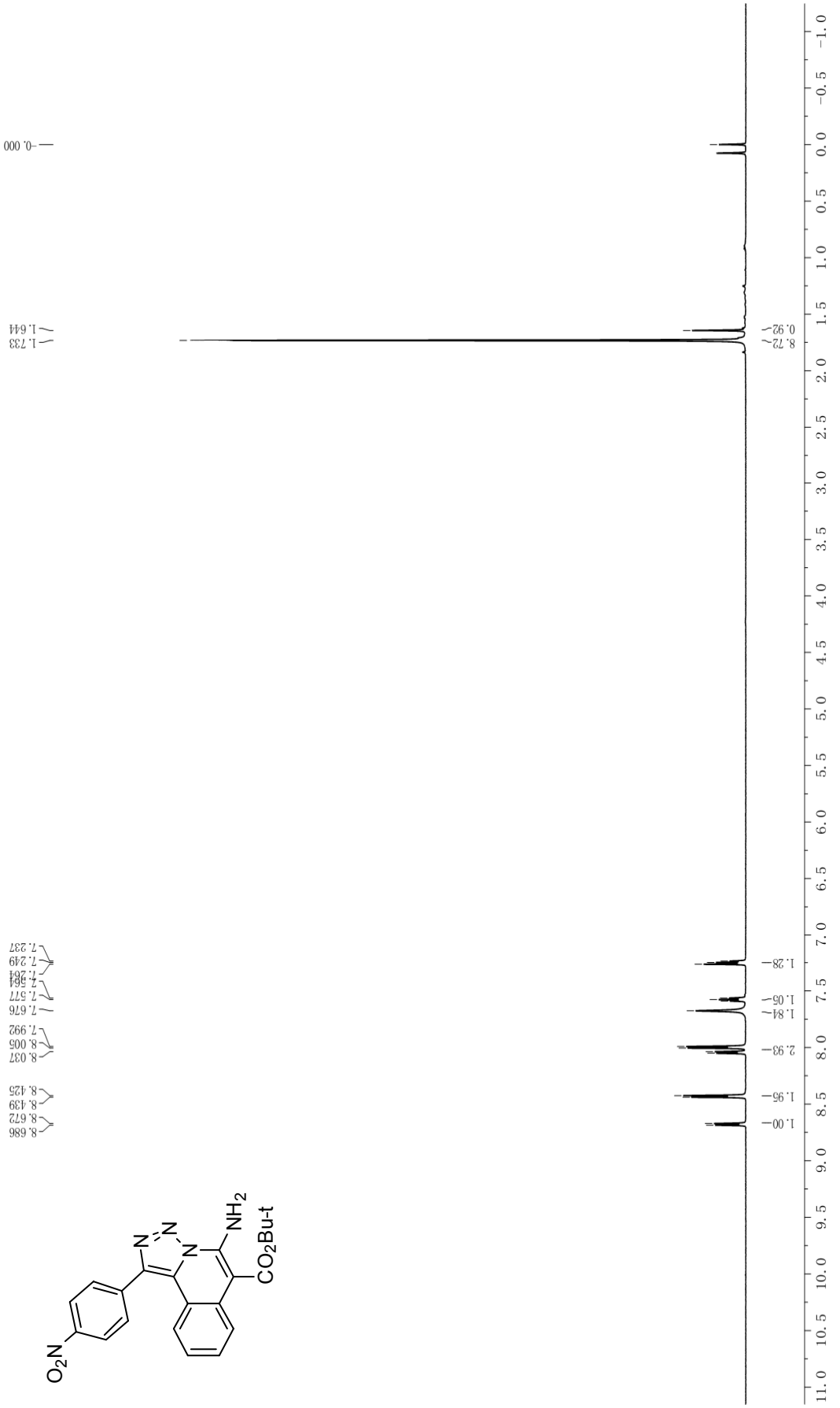


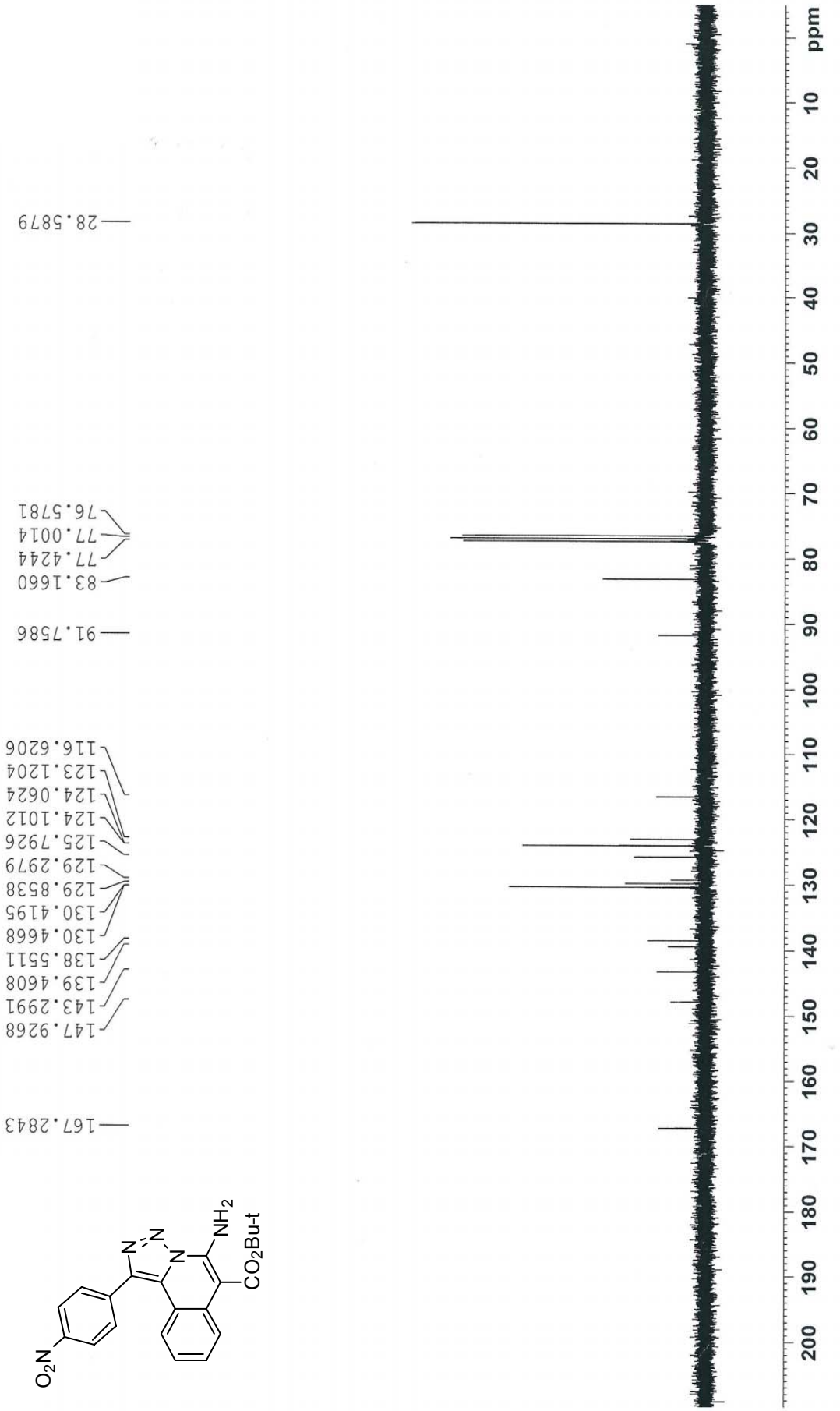


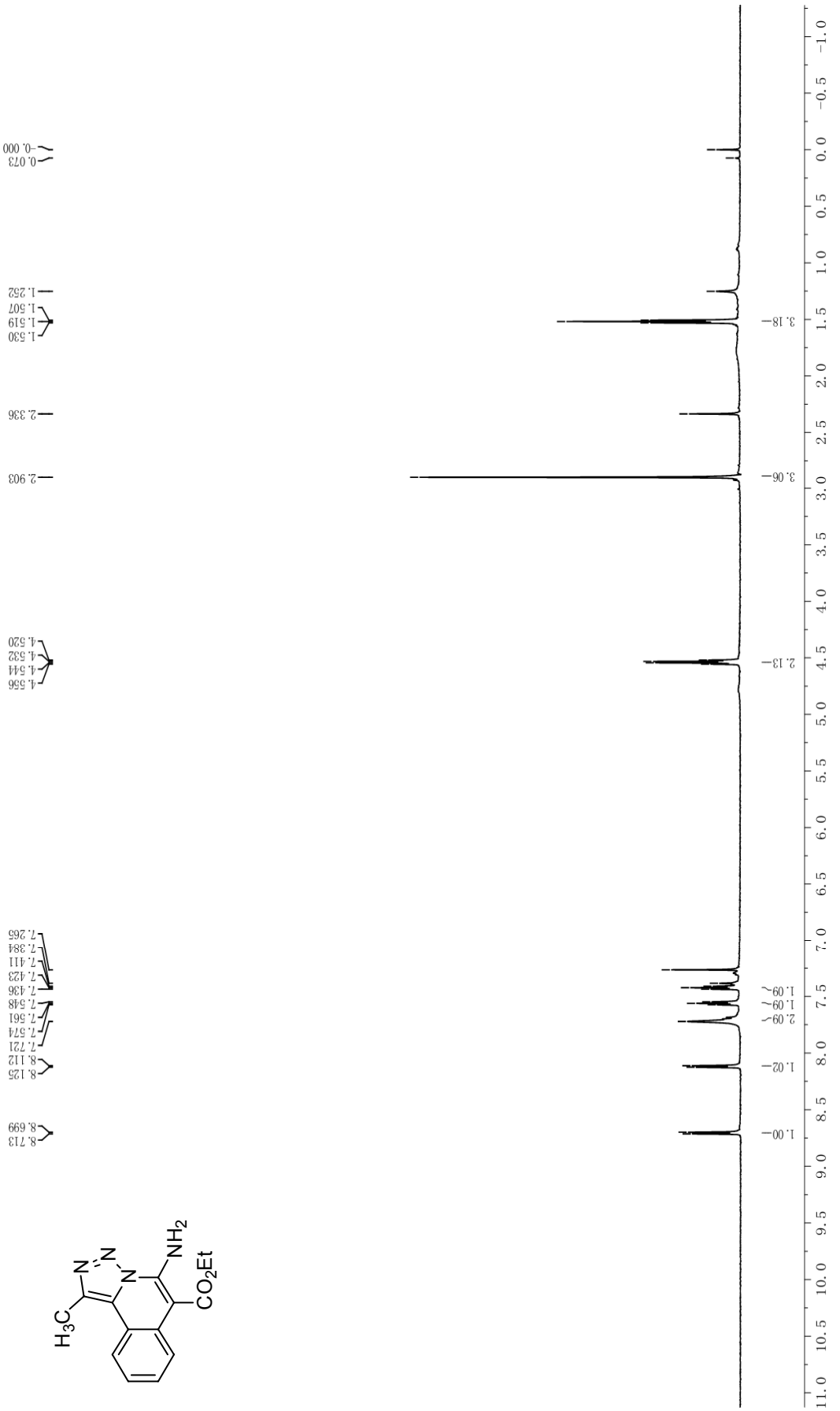


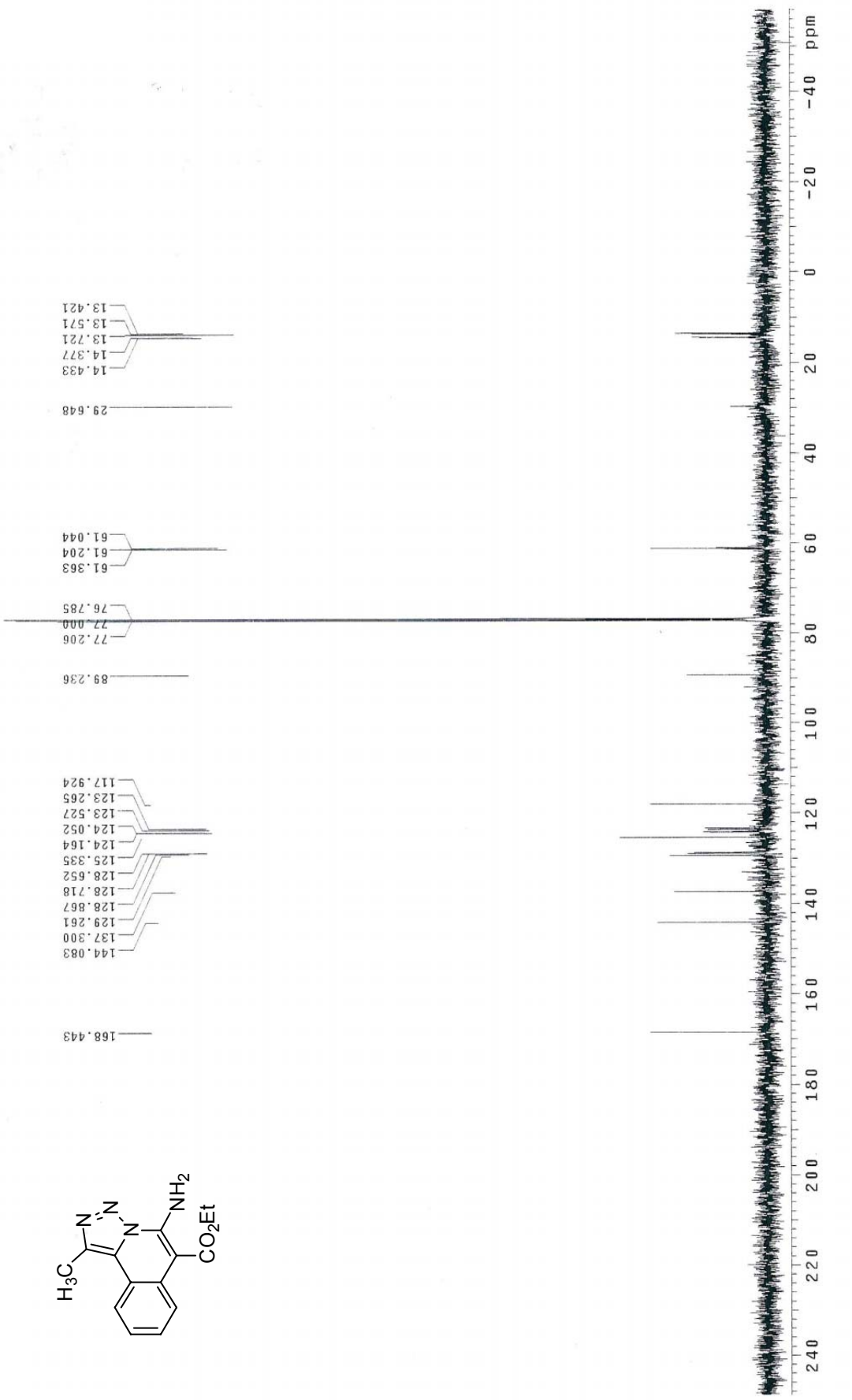


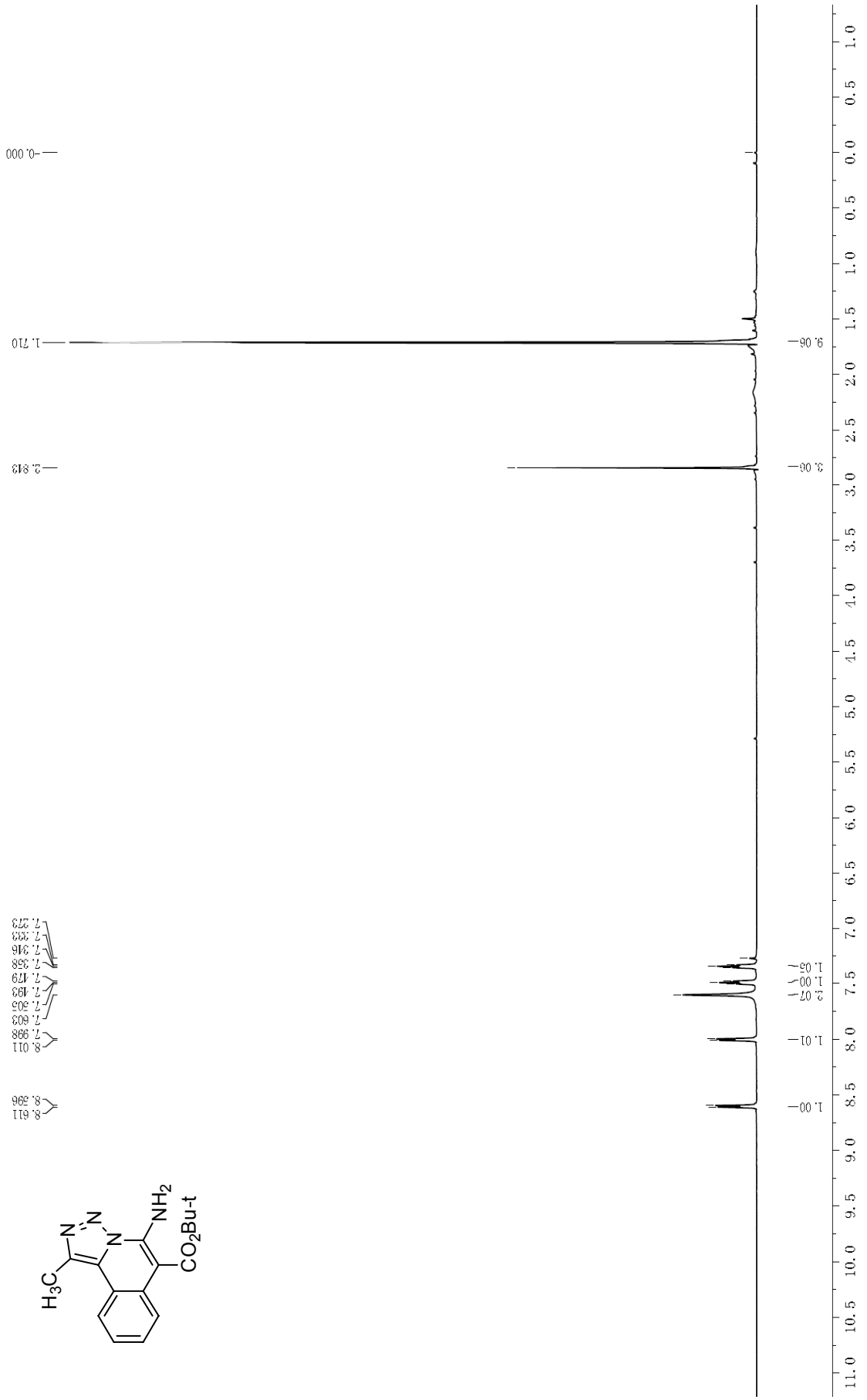


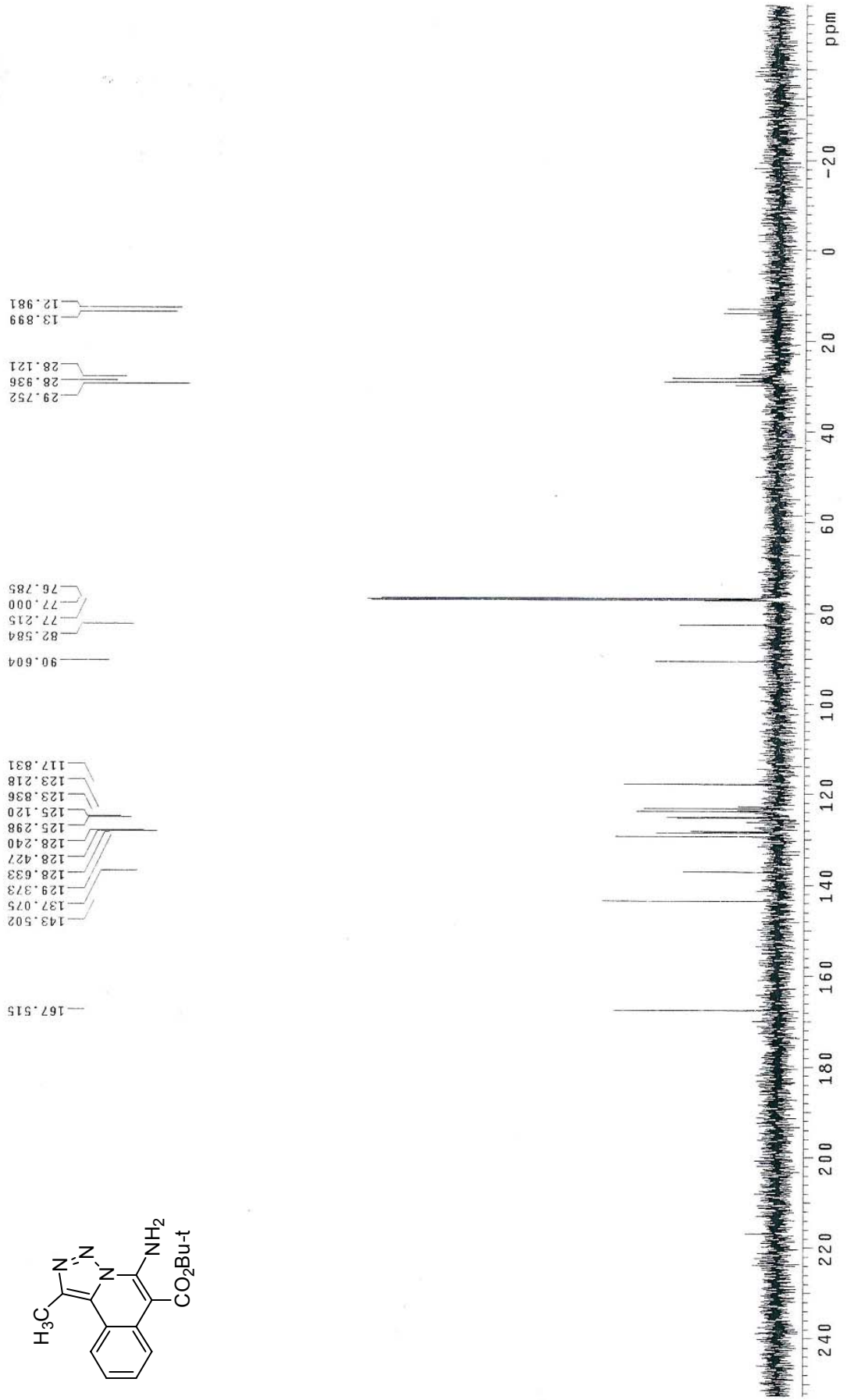


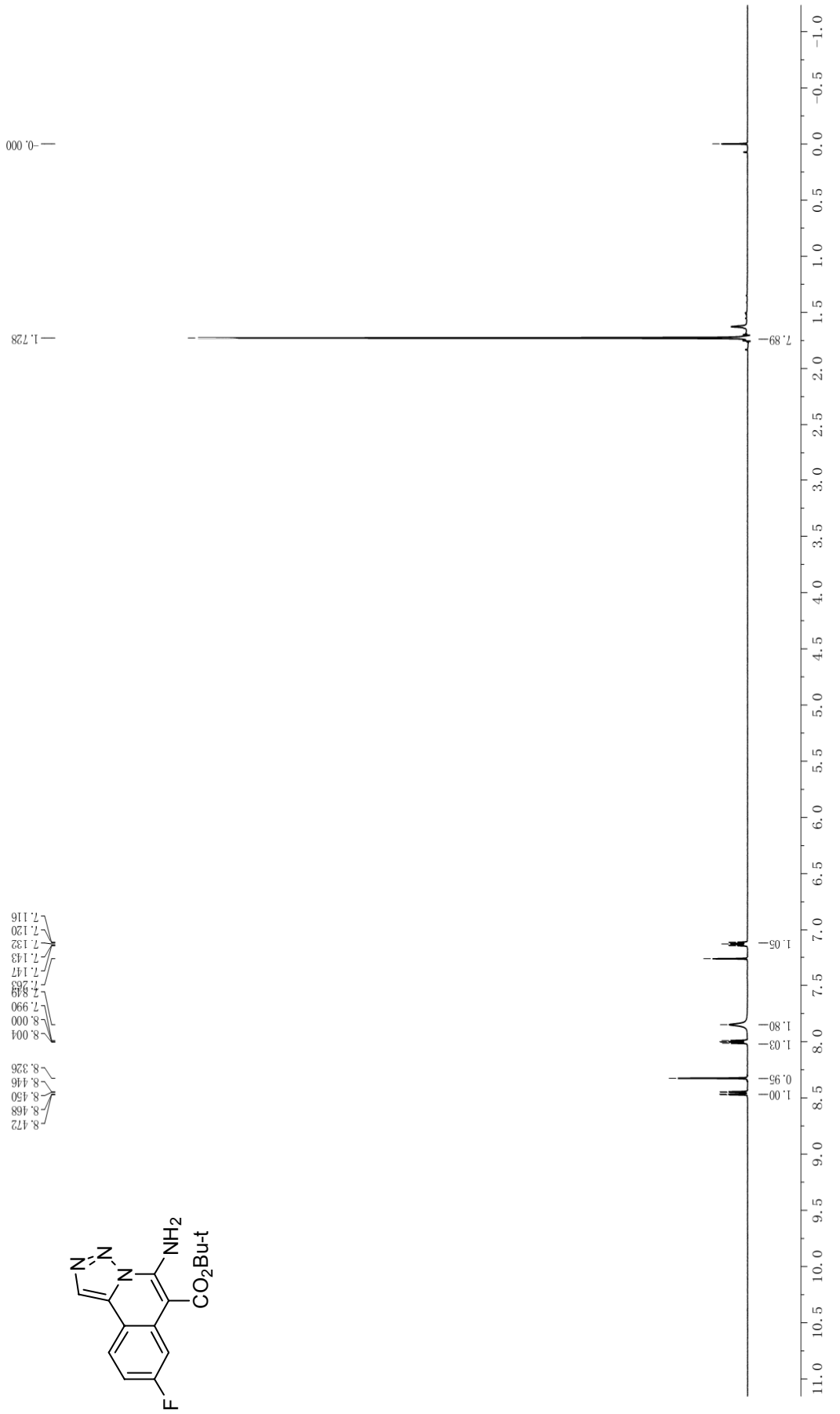


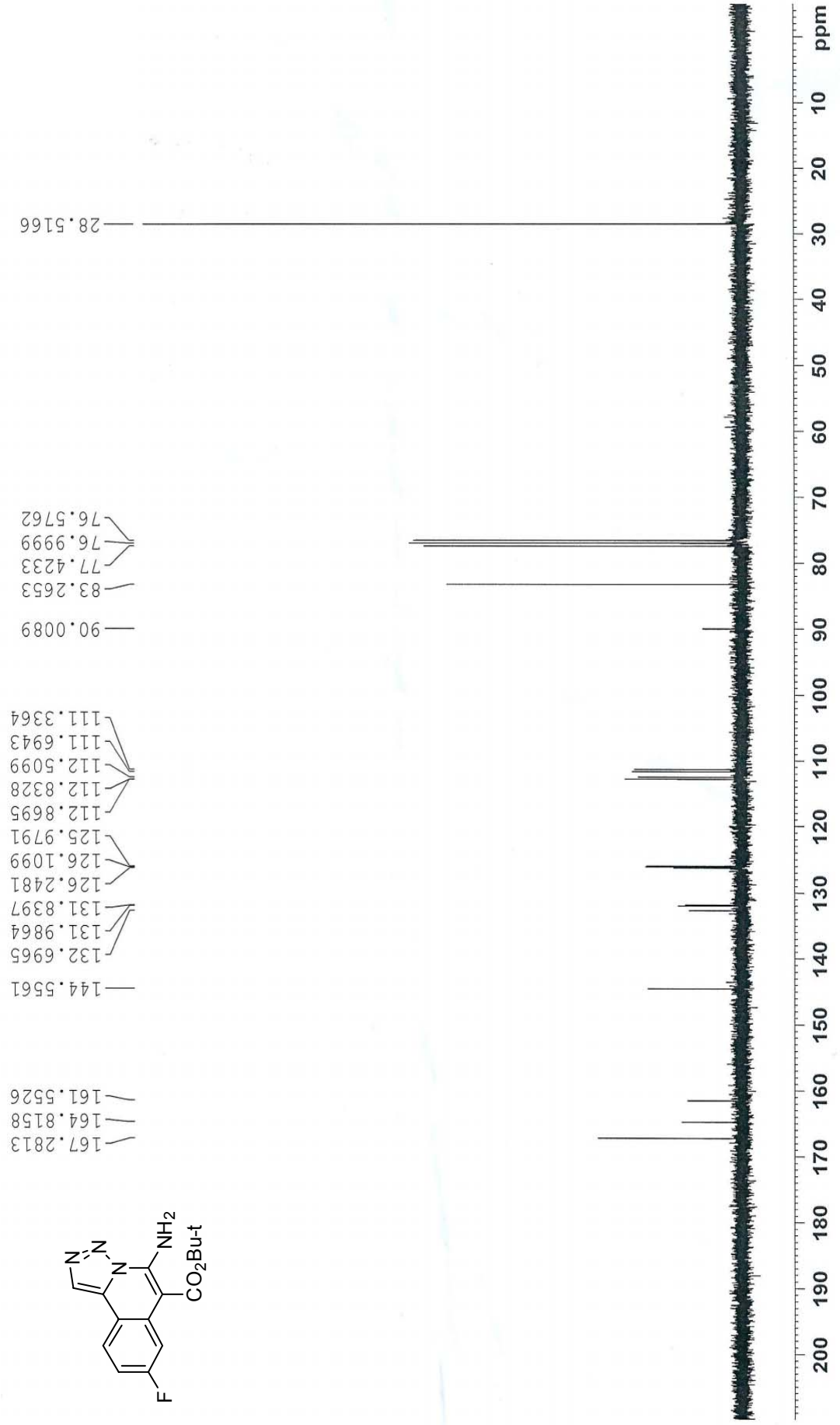


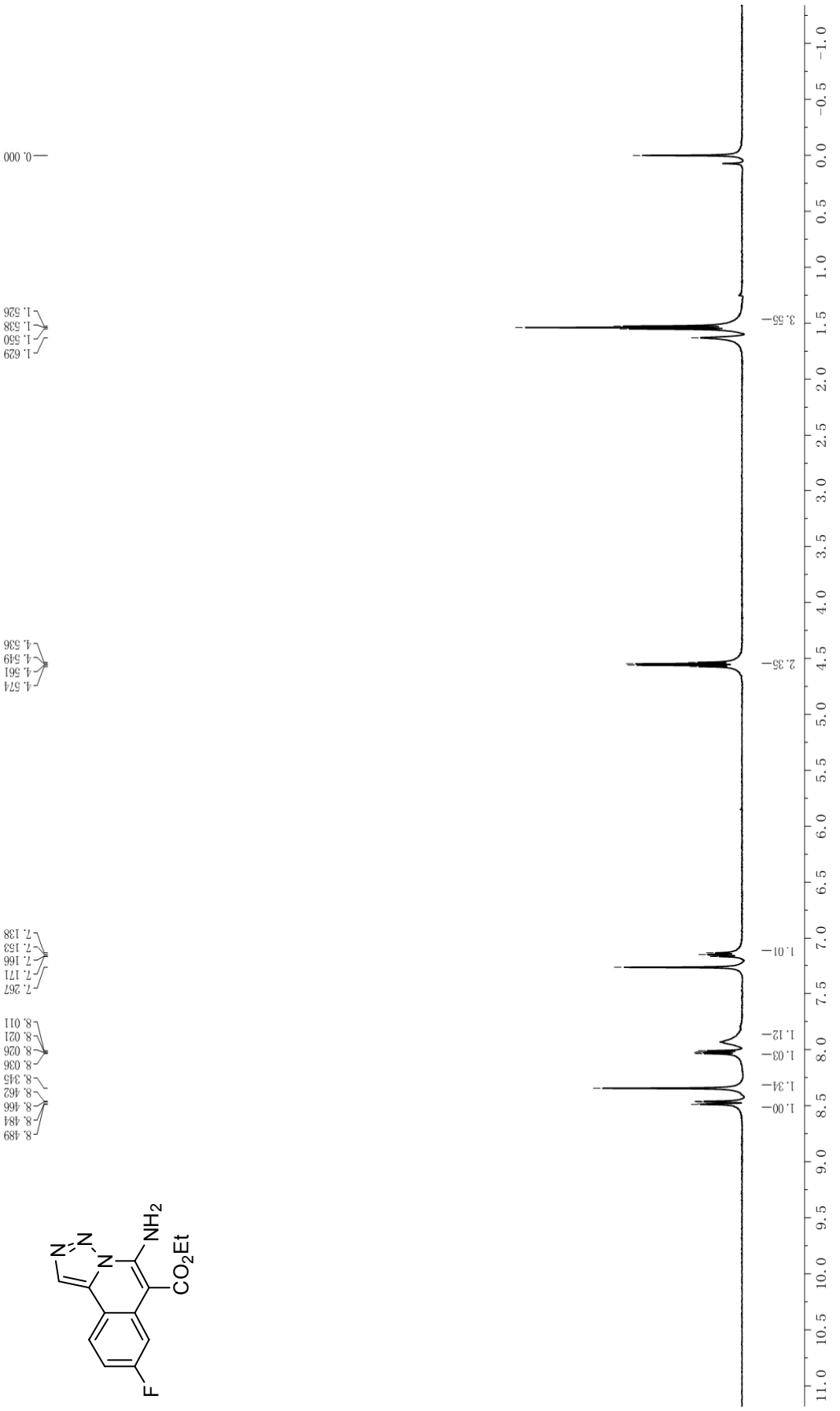


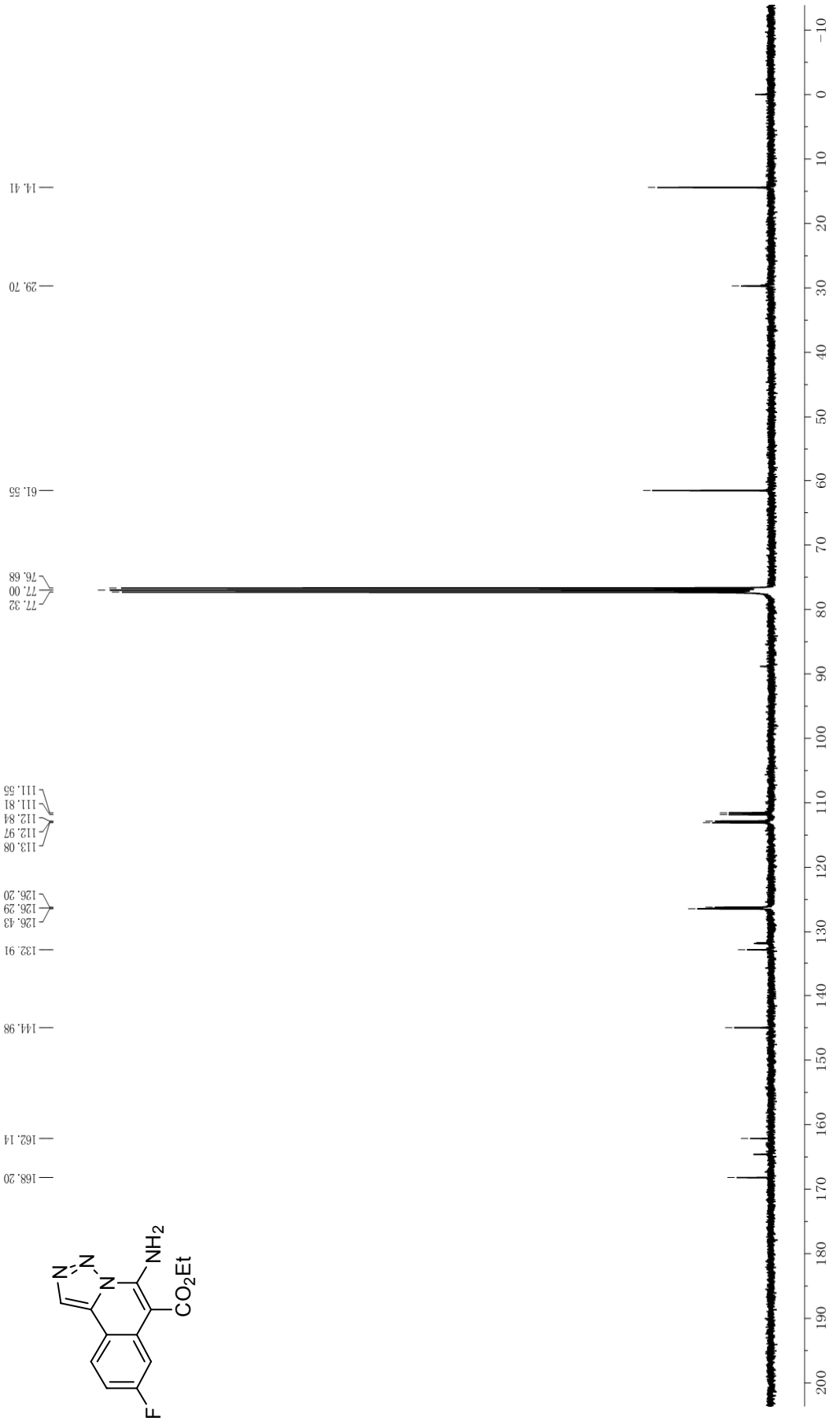


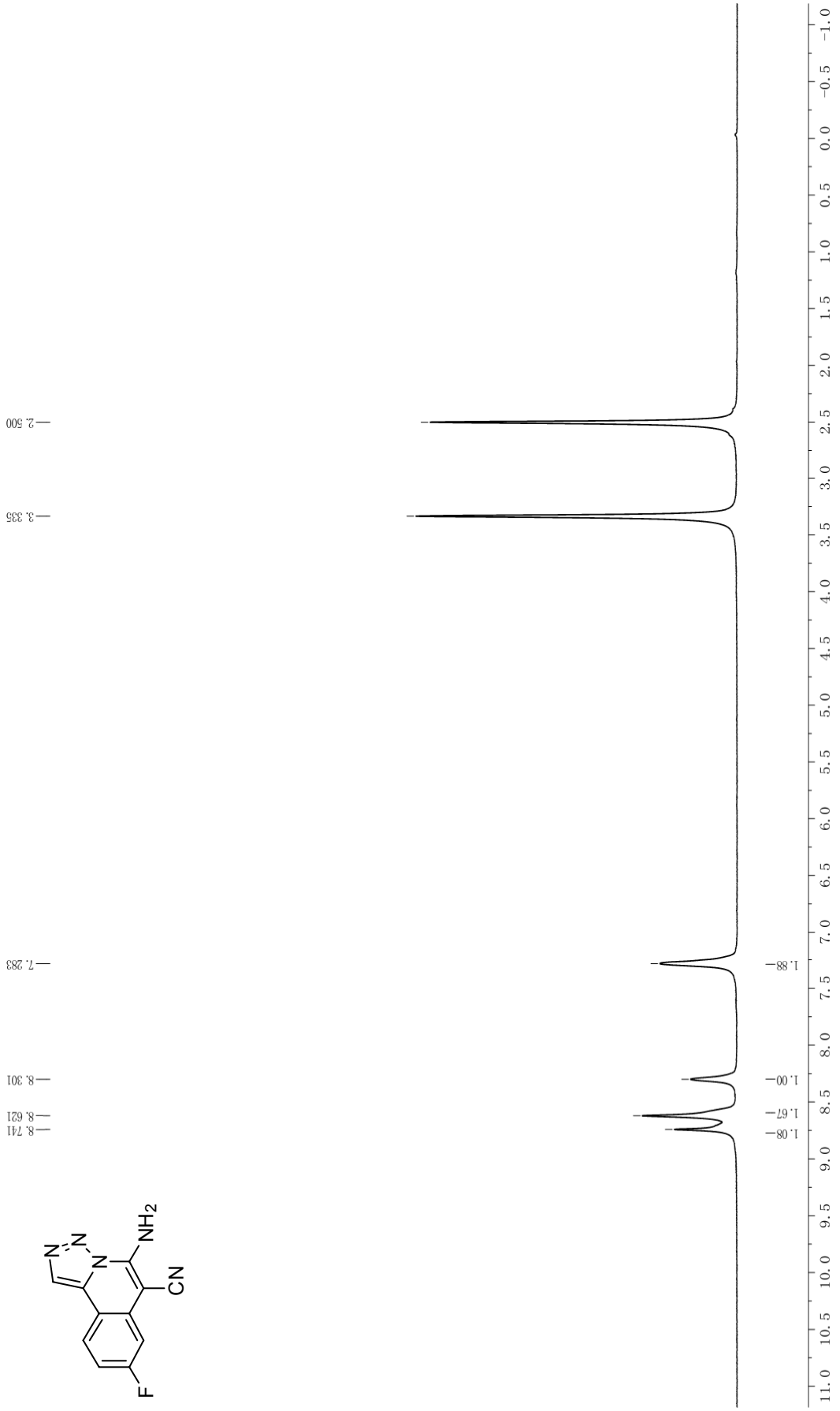


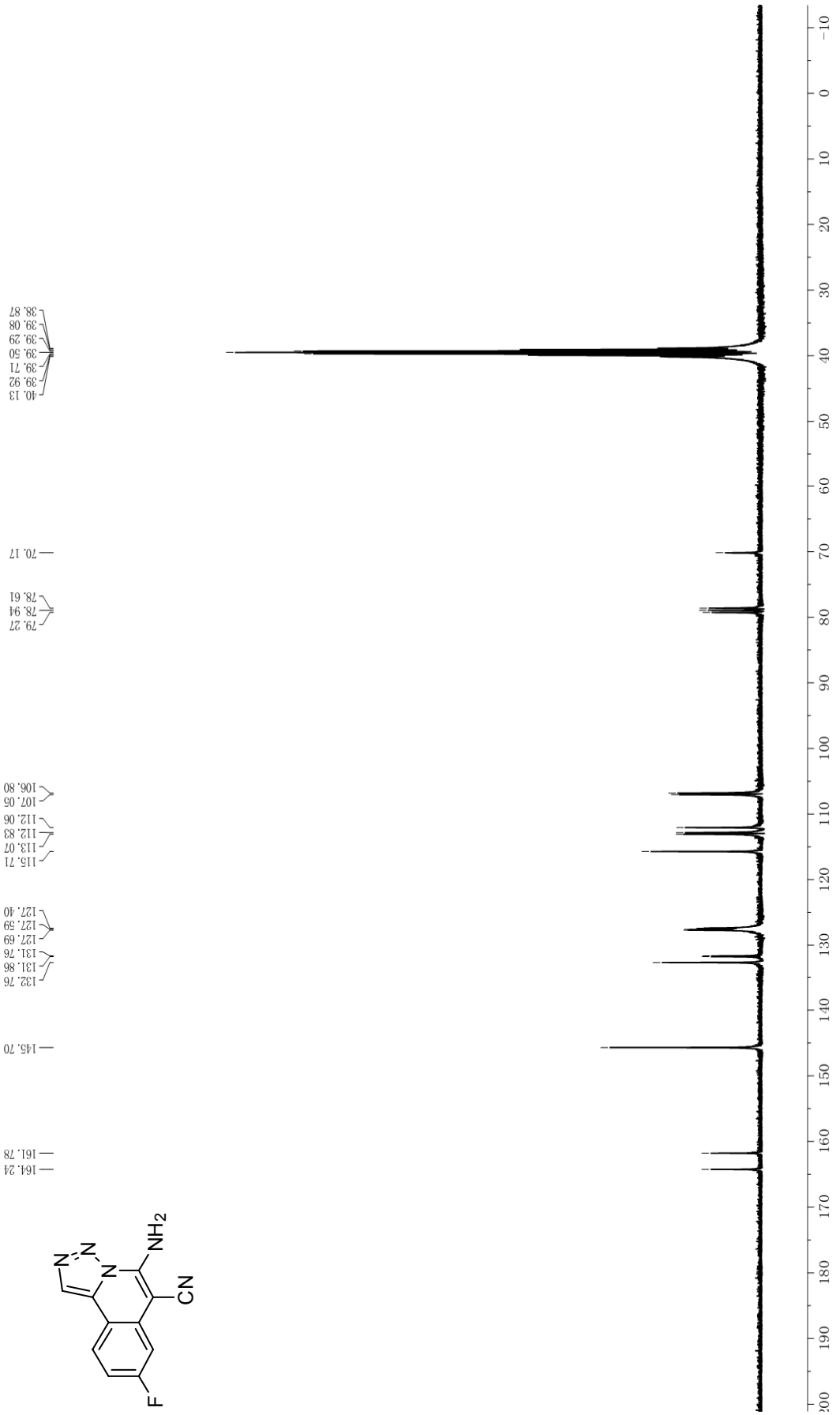


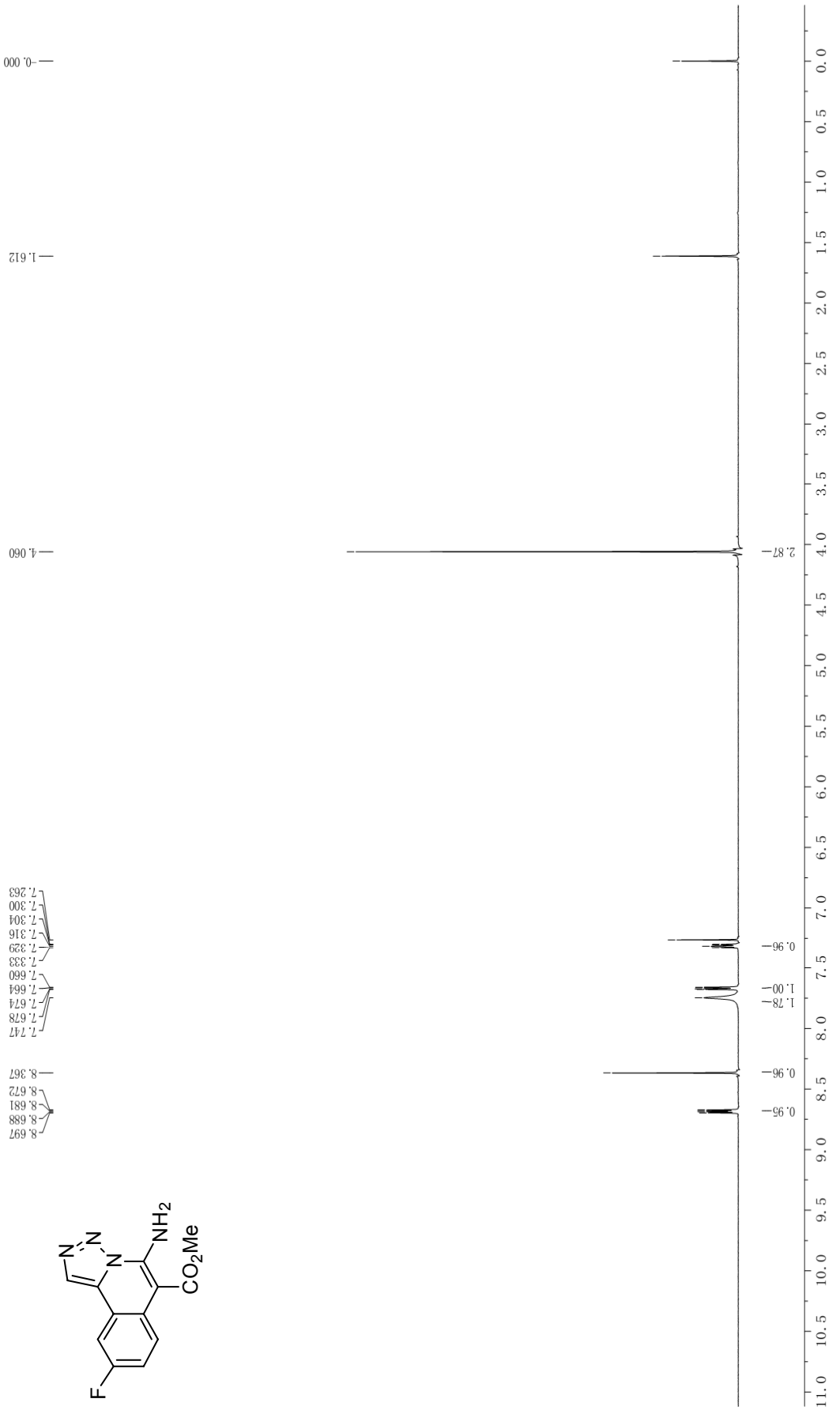


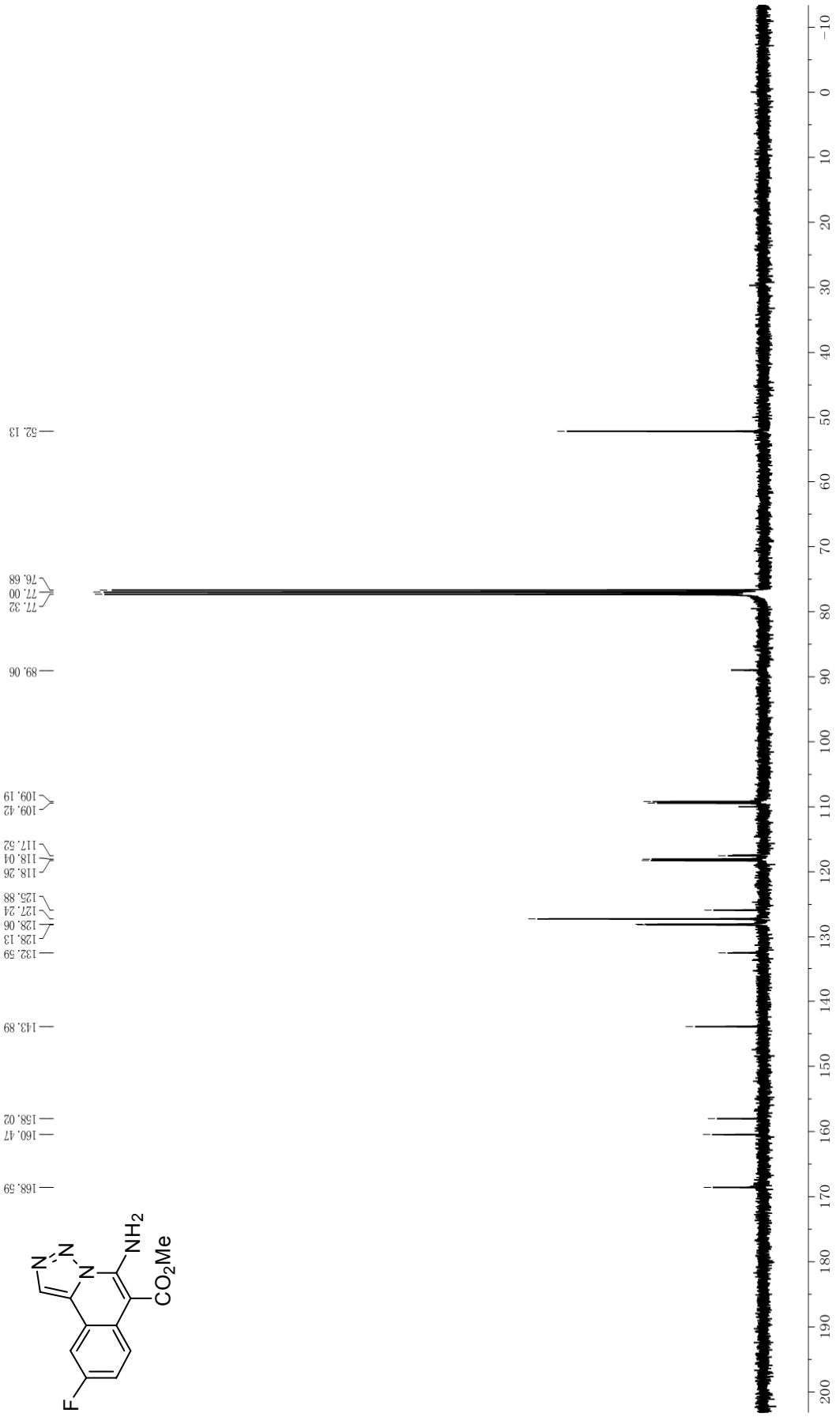


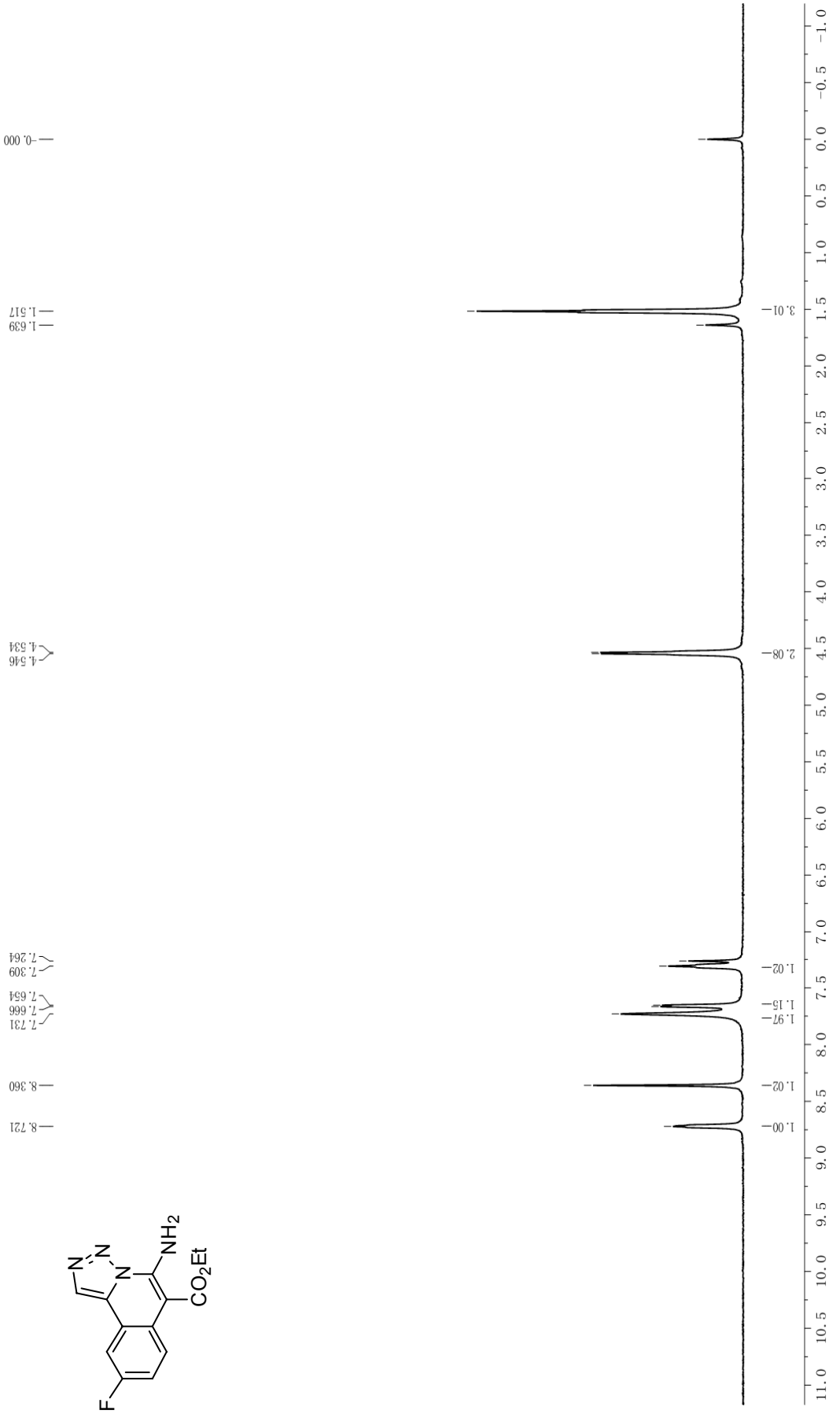


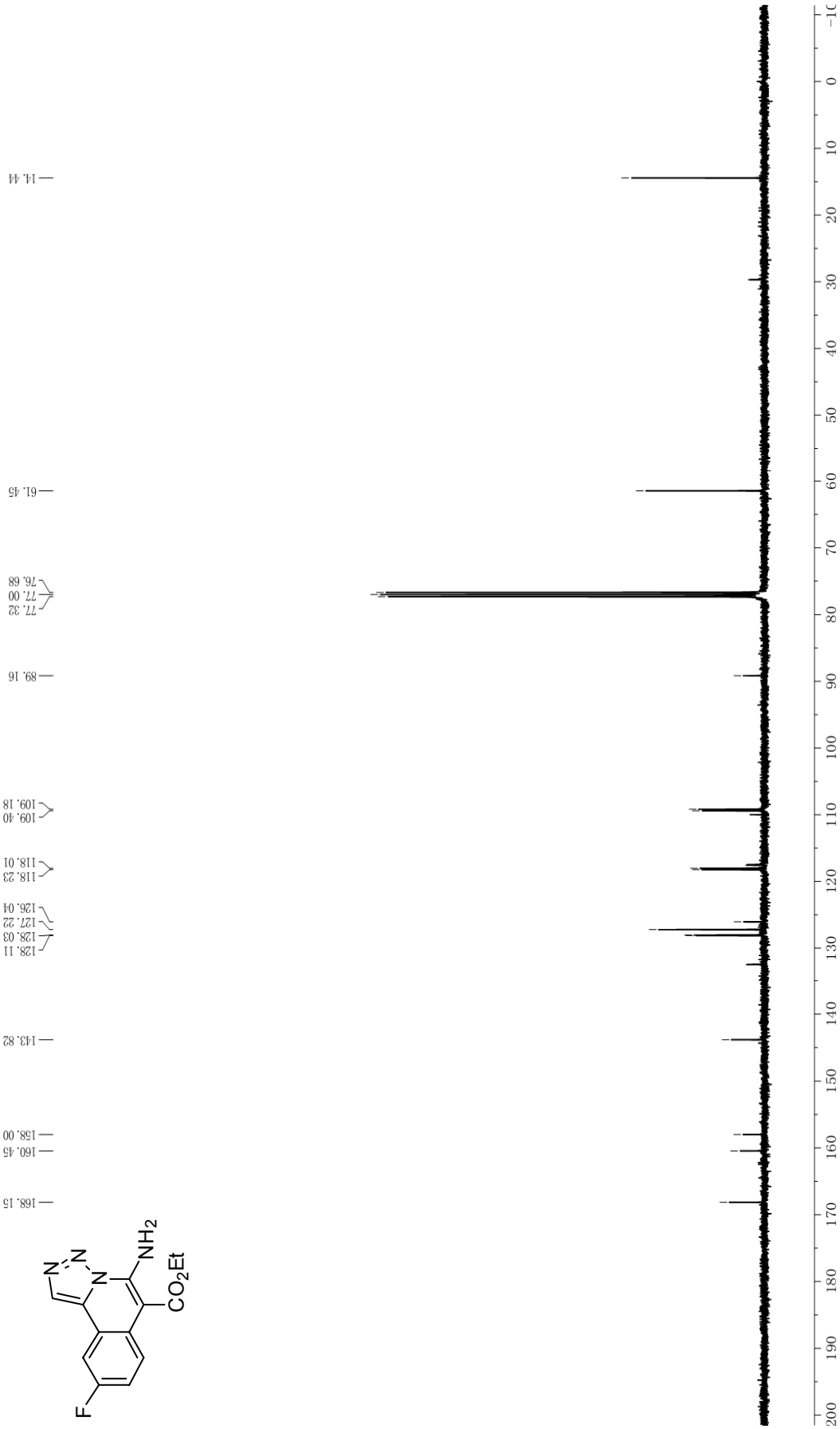


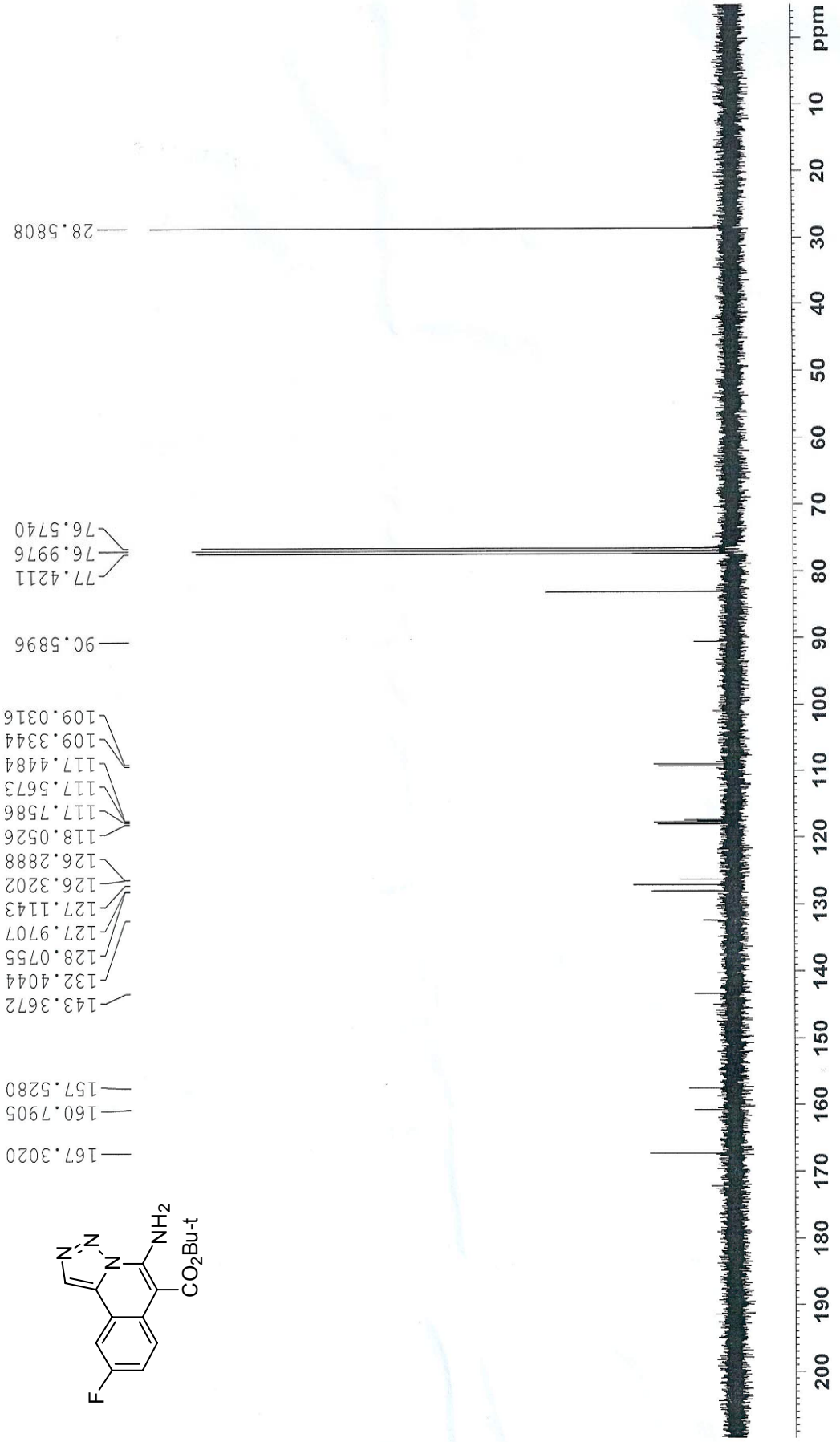


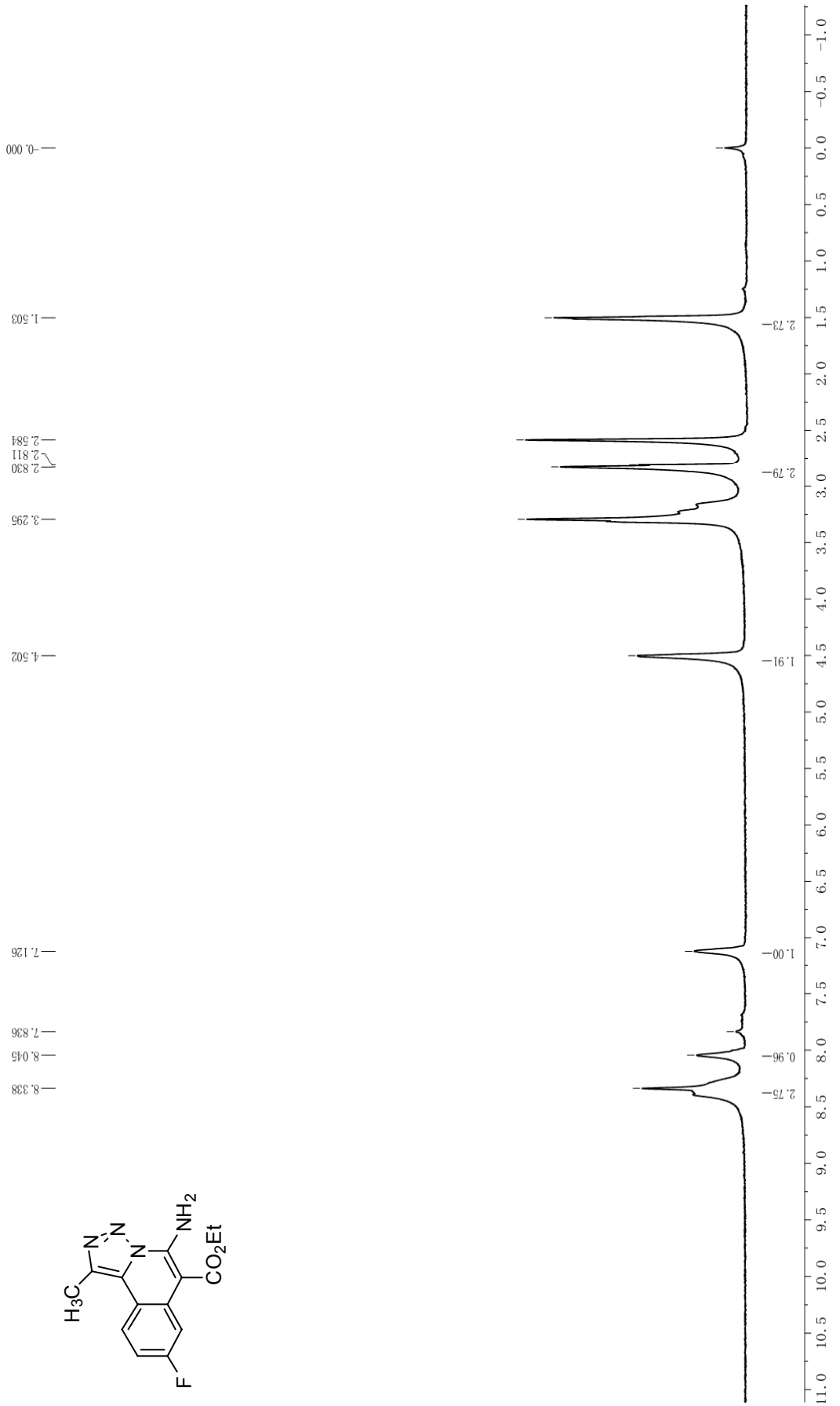


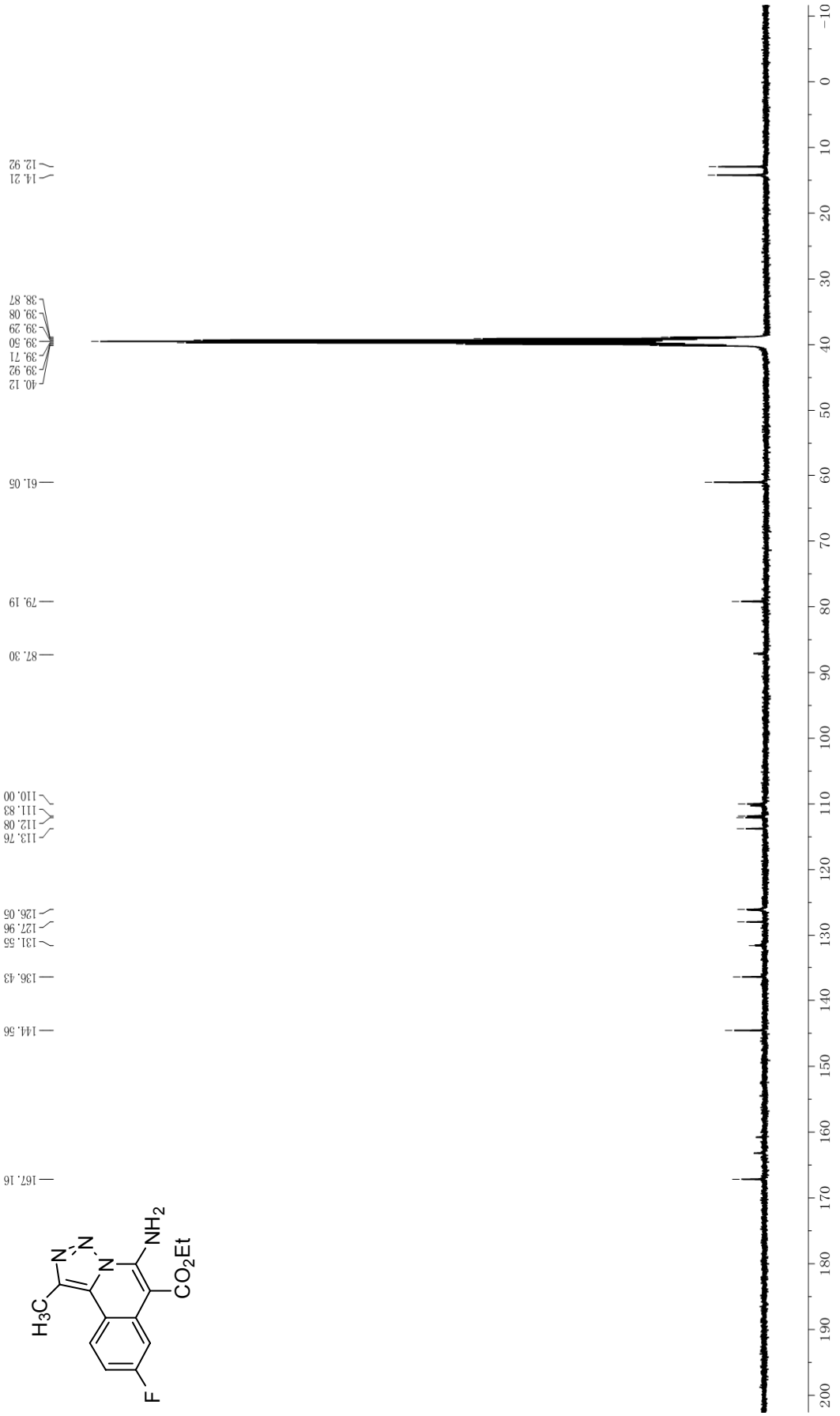


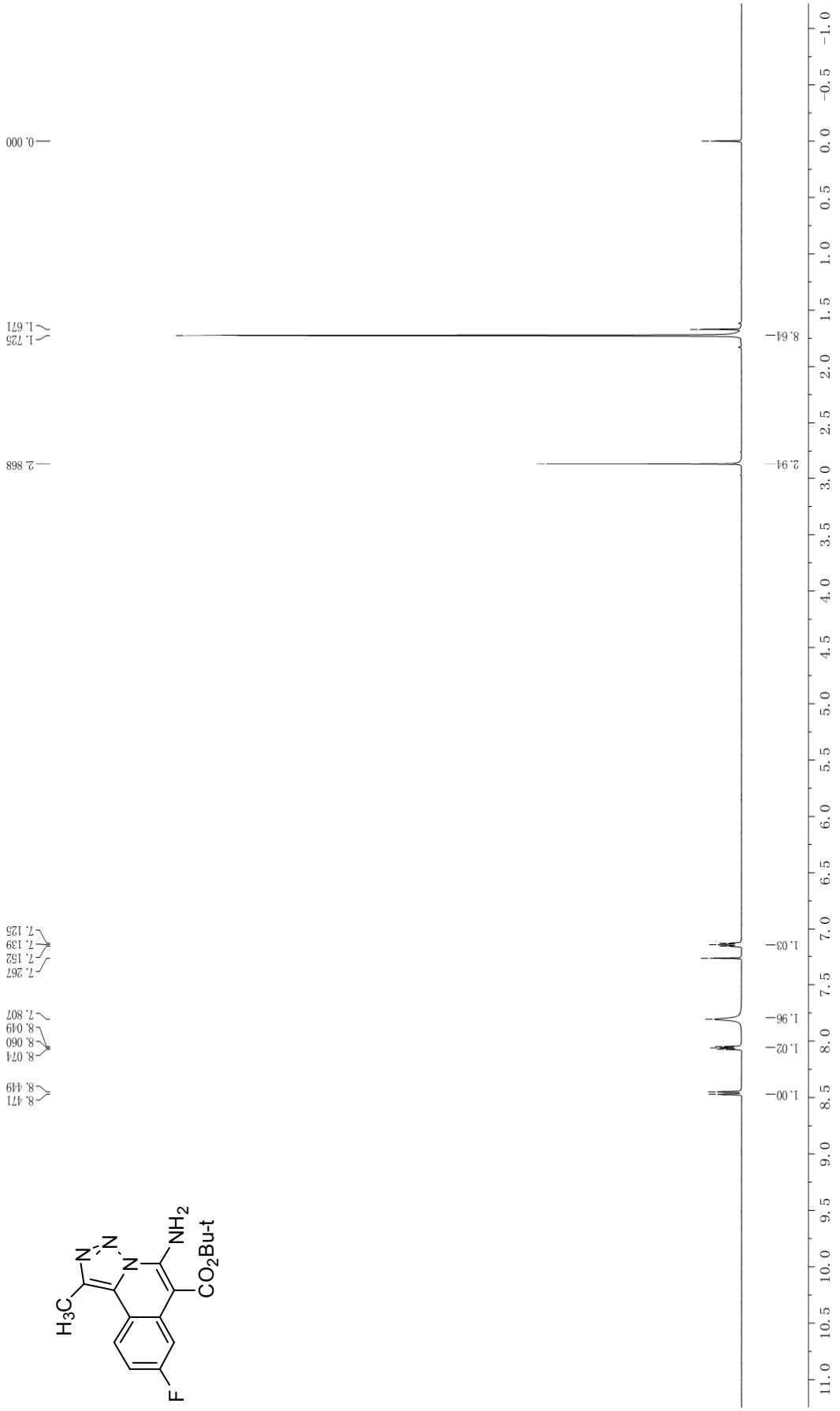


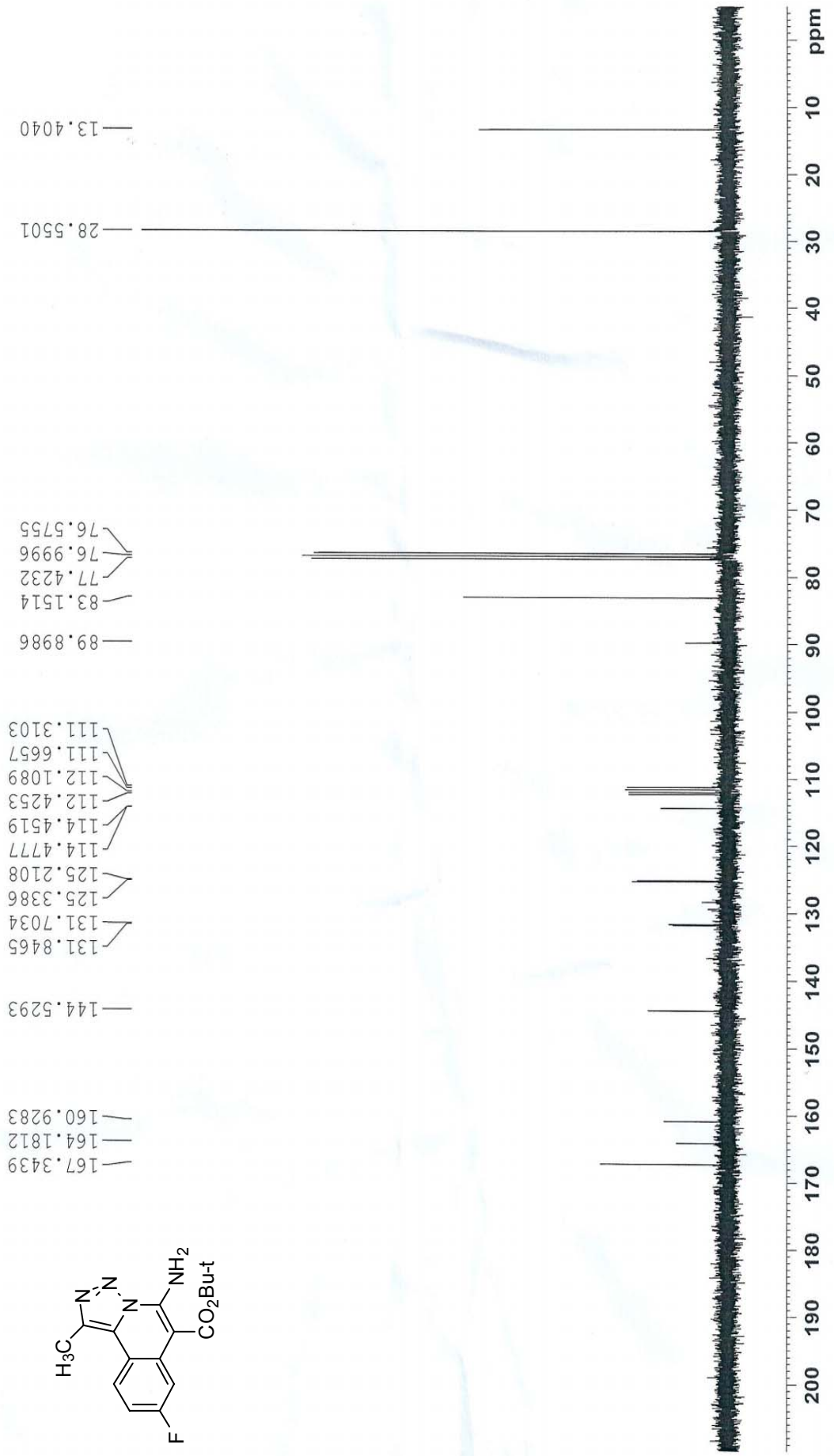


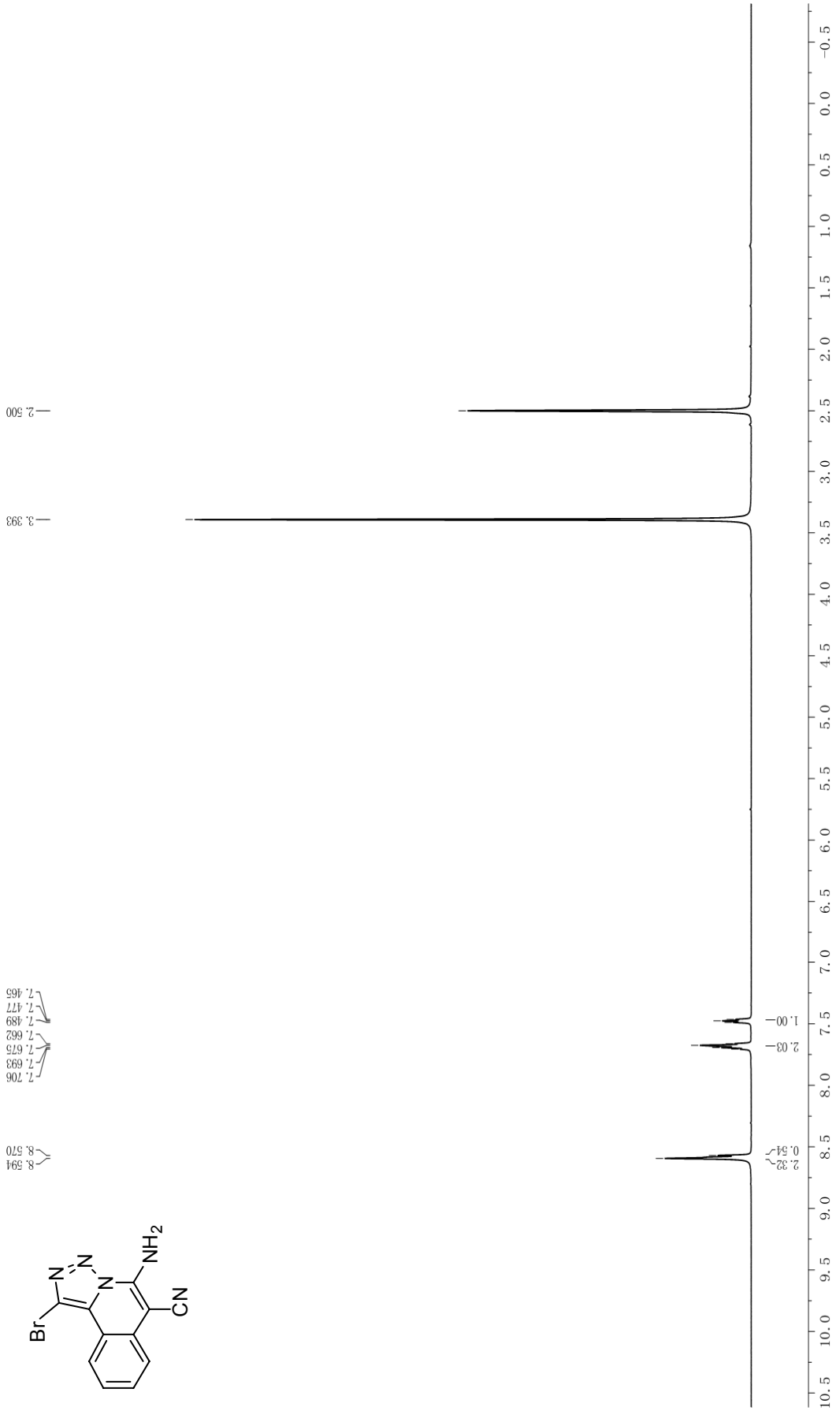


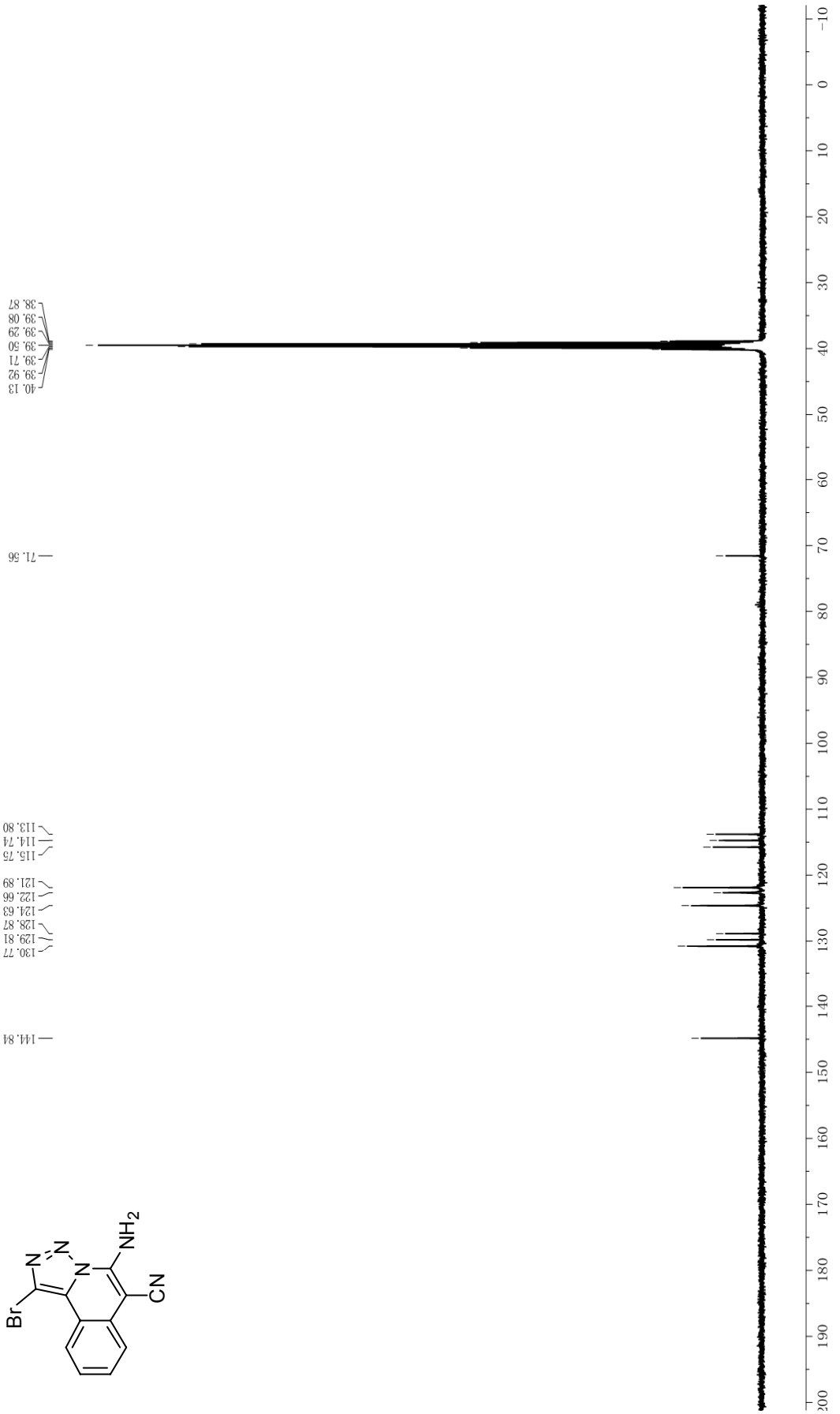


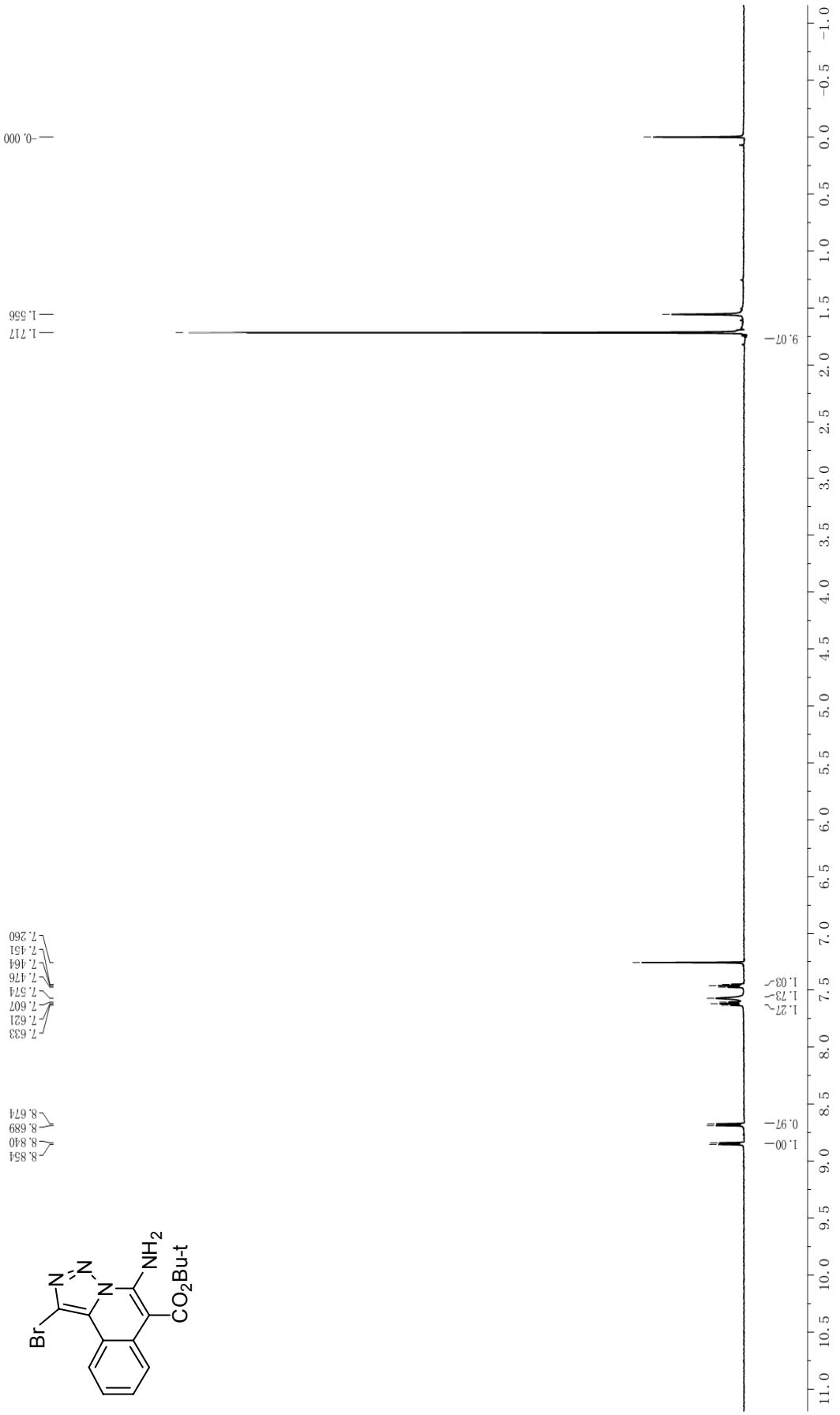


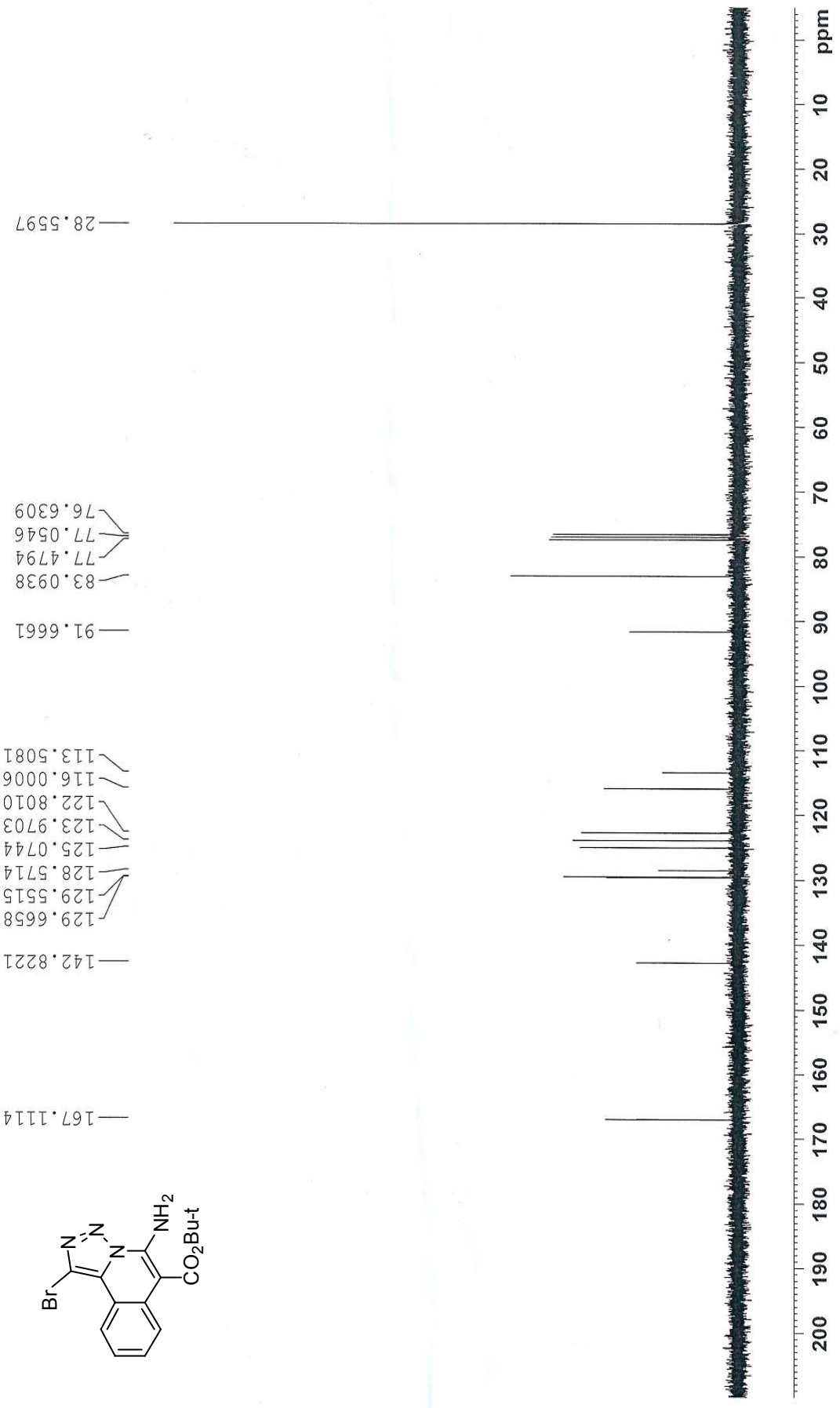


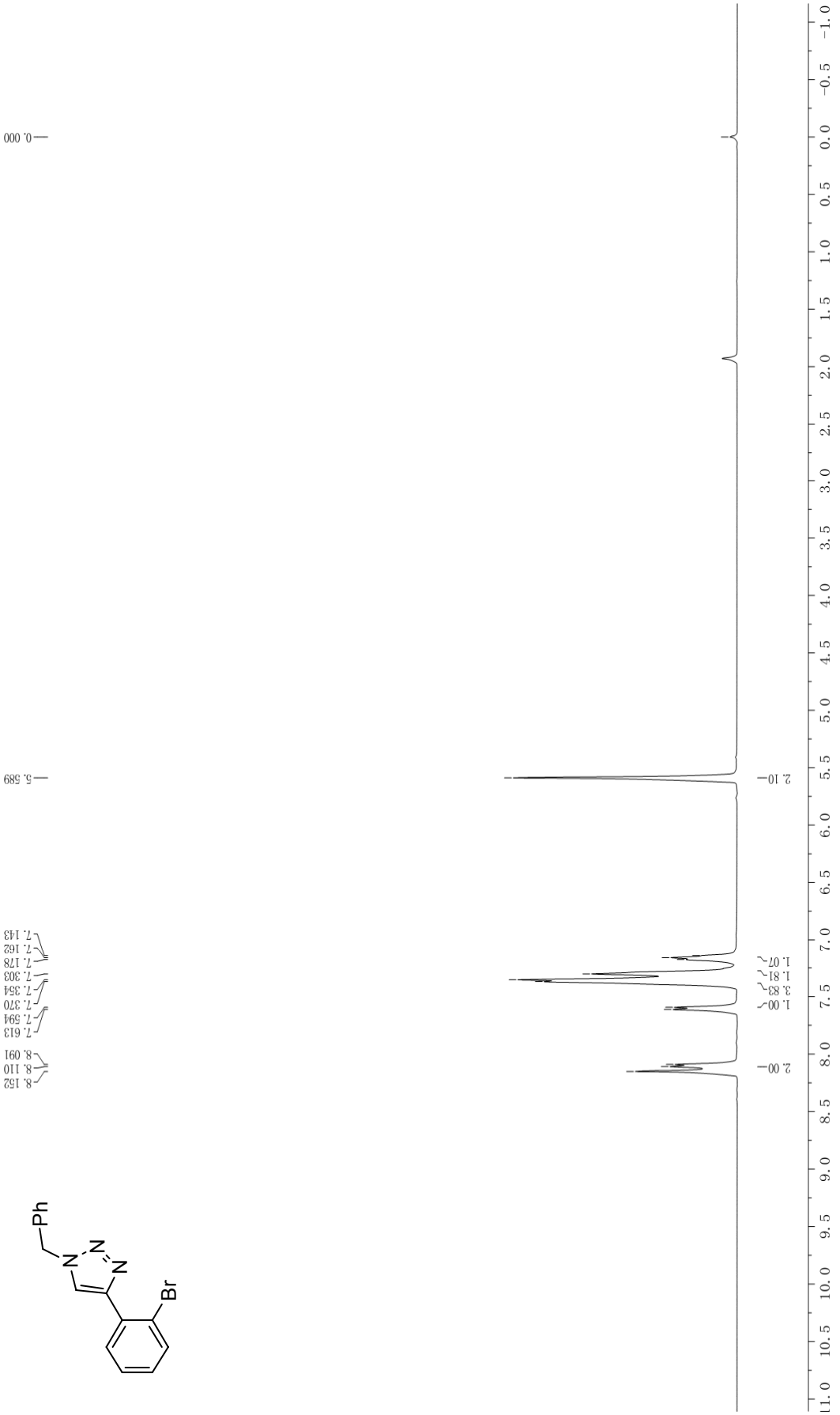


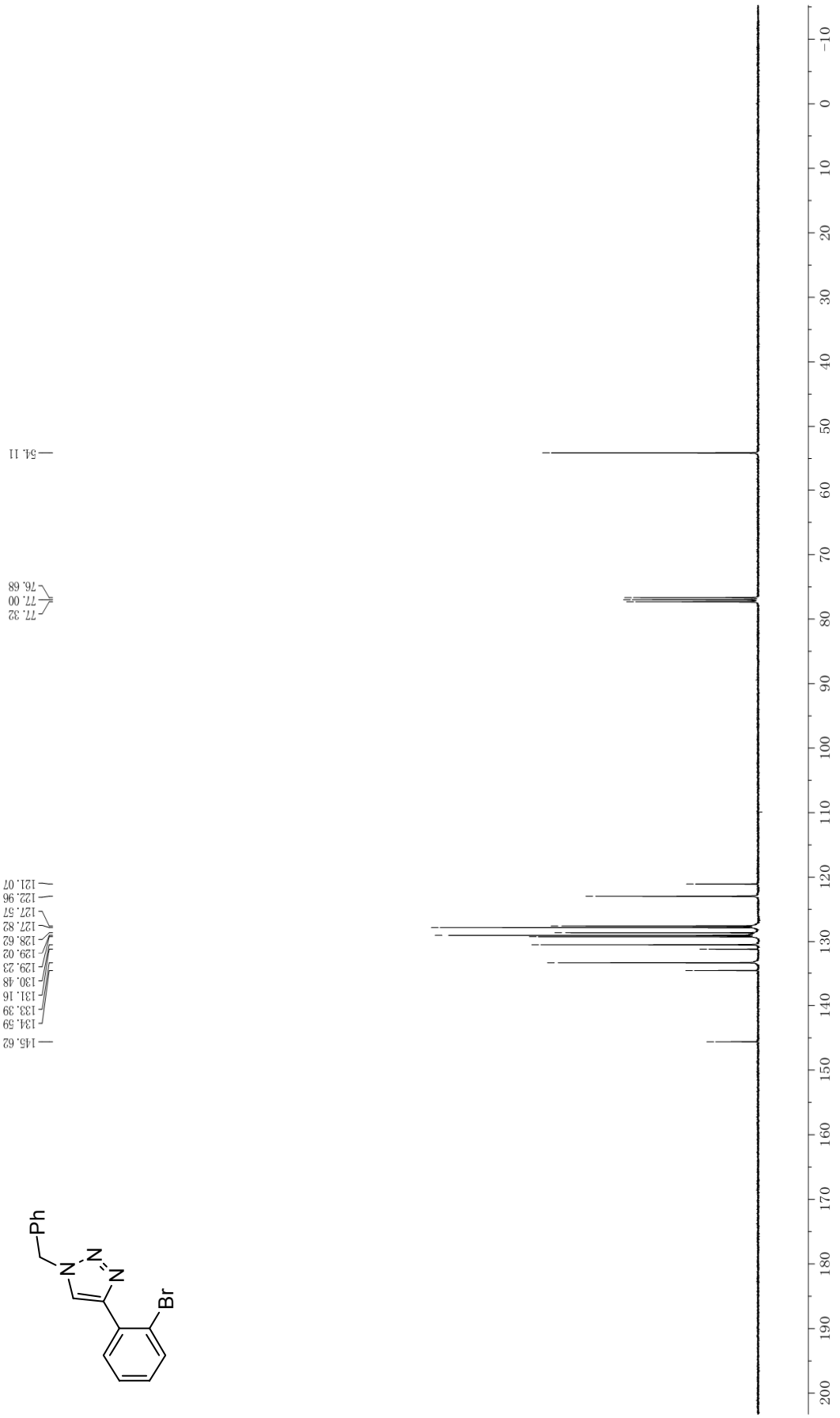


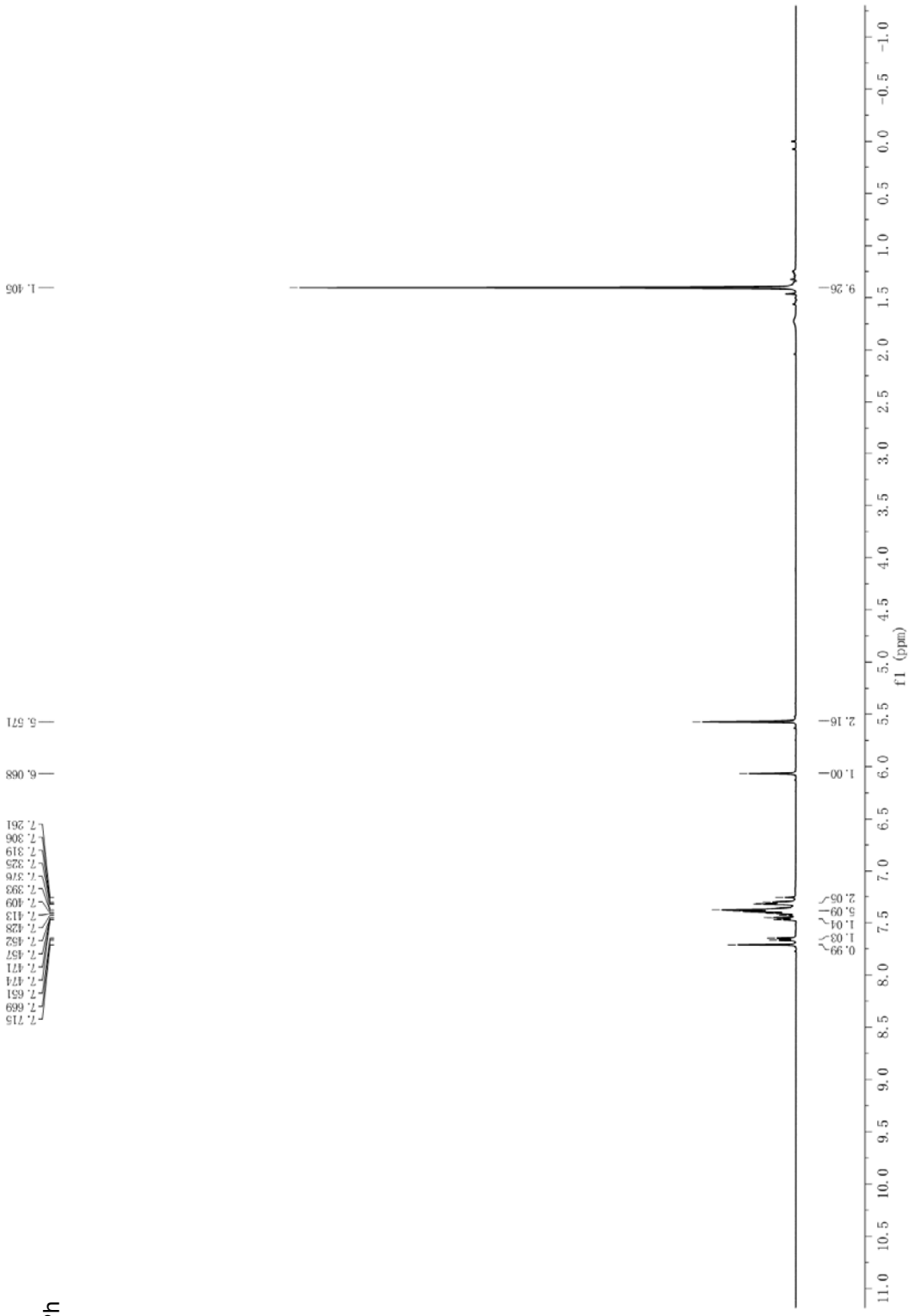


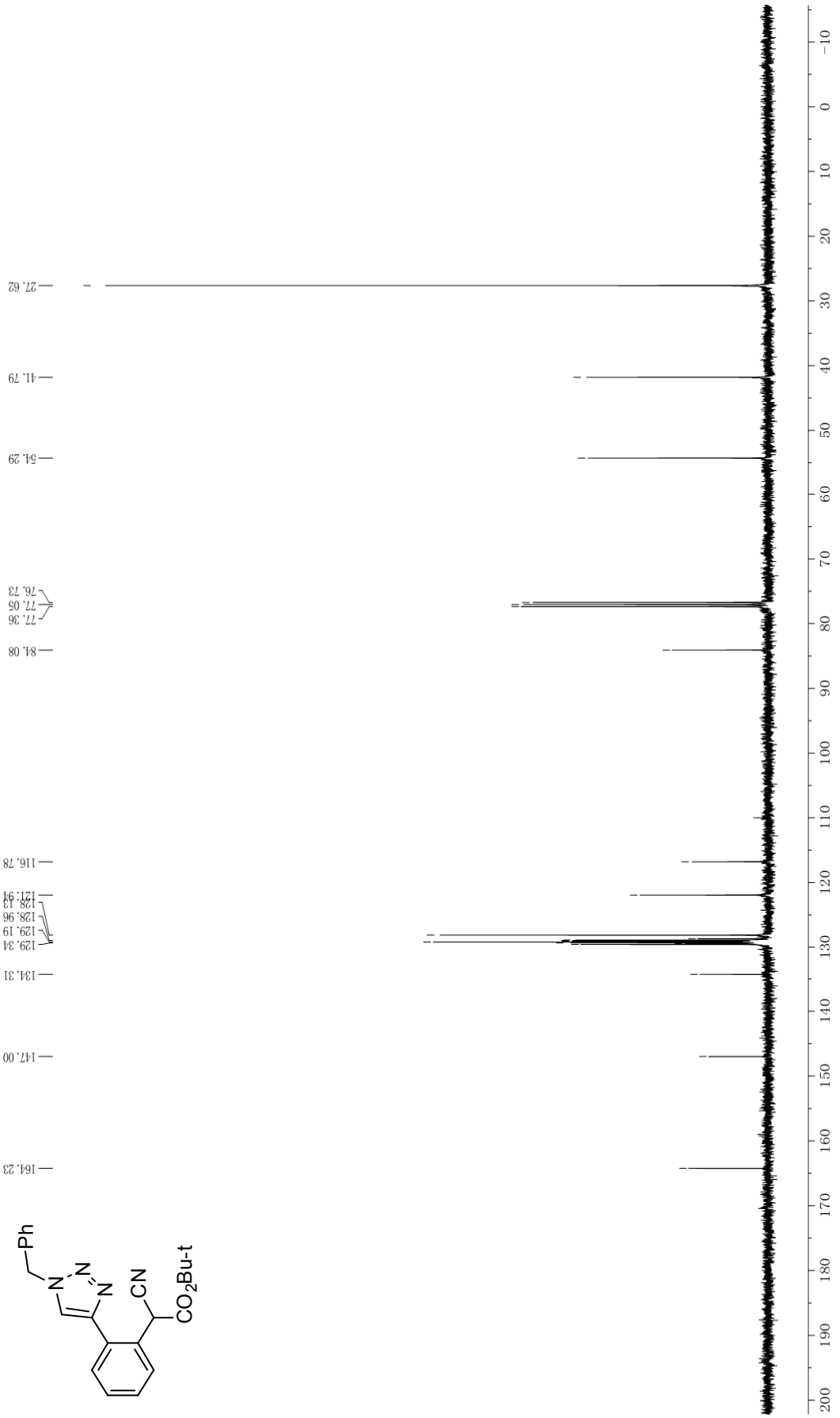










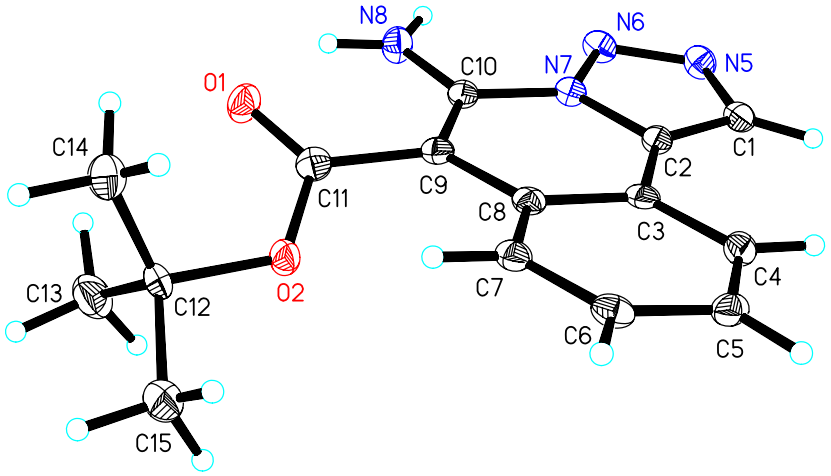


V. X-ray diffraction analysis of compound 3a and 3d.

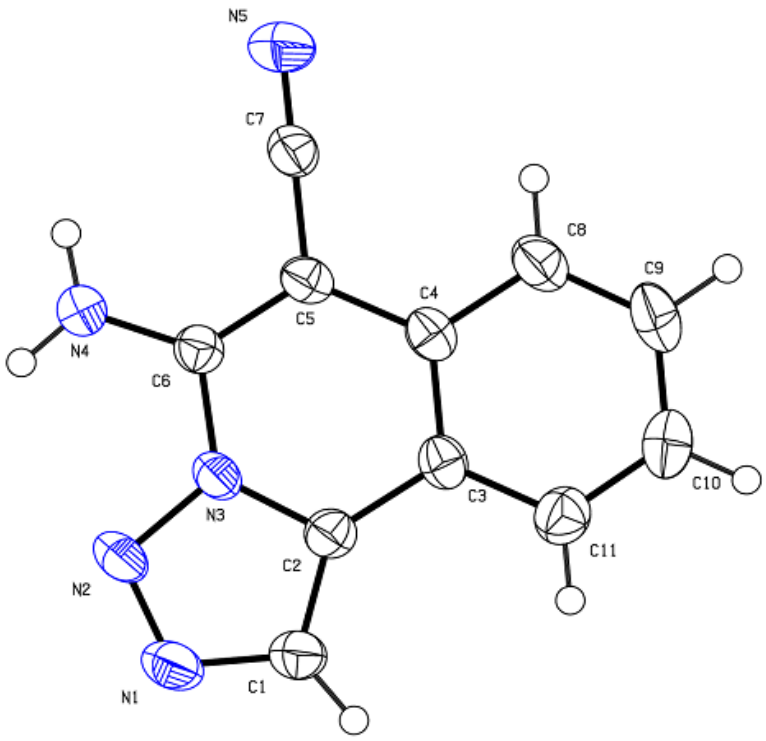
Compound **3a** (25.0 mg) was dissolved in methyl alcohol (5.0 mL) and water, it was crystallized to give crystal as colorless prisms after the solvent was slowly volatilized in 8 days at room temperature.

Compound **3d** (25.0 mg) was dissolved in dichloromethane and petroleum ether (V/V, 1:4), it was crystallized to give crystal as colorless prisms after the solvent was slowly volatilized in 3 days at room temperature.

3a: CCDC number 938029; **3d**: CCDC number 938028.



3a



3d